UNIVERSITY OF
LIVERPOOL

No Halide Scavengers, No Ionic Additives, No Triflates: A "Greener" Palladium-Catalysed Regioselective Heck Arylation of Electron-Rich Olefins

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

Written by

Zeynab Hyder

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For my family,

Father, Mother, Paula and Zerin.

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Publications

"Hydrogen-bond-directed catalysis: Faster, regioselective and cleaner Heck arylation of electron-rich olefins in alcohols" Hyder, Z.; Ruan, J. W.; Xiao, J. L. *Chem: Eur. J.* **2008**, *14*, (18) 5555.

"Ionic liquids as solvent for regioselective arylation of alpha-substituted allylic alcohols by aryl bromides" Liu, S. F.; Thomson, N.; Pettman, A.; Hyder, Z. M.; Mo, J.; Xiao, J. L. *J. Mol. Catal. A: Chem.* **2008**, *279*, (2) 210.

"Palladium-catalysed regiocontrolled internal heteroarylation of electron-rich olefins with heteroaryl halides" Xu, D.; Liu, Z.; Tang, W.; Xu, L.; Hyder, Z.; Xiao, J. L. *Tet. Lett.* **2008**, *49*, (42) 6104.

"Green chemistry: C-C coupling and asymmetric reduction by innovative catalysis" *Prog. Nat. Sci.* Wu, X. F.; Mo, J.; Li, X. H.; Hyder, Z.; Xiao, J. L. **2008**, *18*, (6) 639.

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"Palladium-catalysed direct regioselective synthesis of cyclic ketals from electron-rich olefins and aryl bromides in ionic liquids" Hyder, Z.; Mo, J.; Xiao, J. L. *Adv. Synth. Catal.* **2006**, *348*, (12) 1699.

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Definitions and Abbreviations

Δ	reflux
%	percent
ε_r	dielectric constant
μ	dipole moment
α	*alpha*
β	*beta*
δ	chemical shift (delta)
o	*ortho*
m	*meta*
p	*para*
aq.	Aqueous
b.p	boiling point
[bmim] [BF4]	1-butyl-3-methylimidazolium tetrafluoroborate
^{n}Bu	*n*-butyl
°C	degree celsius
^{13}C	carbon-13
C_i	concentration of ion, *i*
ca.	circa (approximately)
$CHCl_3$	chloroform
CI	chemical ionization
conv.	Conversion
DCM	dichloromethane
DMA	*N*,*N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
DOM	dissolved organic matter
DPPP	1,3-bis(diphenylphosphino)propane
EHS	environmental, health and safety hazard
E_T^N	"measure of solvent polarity"
GC	gas chromatography

h	hour(s)
HAP	hazardous air pollutants
H-BD	hydrogen-bond donor
HBP	Herrmann-Beller palladacycle
HMPA	hexamethylphosphoramide
$[HNEt_3][BF_4]$	triethylammoniumtetrafluoroborate
$[H_2NiPr_2][BF_4]$	diisopropylammoniumtetrafluoroborate
I	ionic strength
L	litre
LCA	life cycle assessment
mg	milligram
MHz	megahertz
Min	minute(s)
mL	millilitre
MMP	matrix metalloprotease
mol	mole
MW	microwave
Na_2SO4	sodium sulphate
NMP	*N*-methylpyrrolidone
OTf^-	triflate
OMs	mesylate
OAc	acetate
OTs	tosylate
PGM	platinum group metals
ppm	parts per million
^iPrOH	isopropanol
PSR	persistence and spatial range
TBAB	tetrabutylammonium bromide
THF	tetrahydrofuran
TLC	thin Layer Chromatography
TMS	tetramethylsilane
TOF	turnover frequency
TON	turnover number
TPPTS	$p(C_6H_4\text{-}SO_3Na)_3\cdot 3H_2O$ (ligand)

VOC	volatile organic compound
Z_i	charge of ion, *i*

No Halide Scavengers, No Ionic Additives, No Triflates: A "Greener" Palladium-Catalysed Regioselective Heck Arylation of Electron-Rich Olefins

Abstract

The successful arylation of electron-rich olefins by aryl bromides is described, producing a range of of 5-membered and 7-membered aryl ketals, aryl ketones and aryl enamides were synthesied in high yields with excellent regioselectivity toward the internal α-position of the olefin, under a Pd-DPPP catalyst system. The reaction is deemed "green" as it avoids the use of solvents which are currently on the "solvent blacklist" (DMSO, DMF, hexane) which are commonly employed in heck reactions, and replacing them with more benign media. The Heck arylation of electron-rich olefins usually leads to a mixture of branched and linear products, a problem that is solved by the addition of halide scavengers, ionic additives or using aryl triflates. The reactions described in this thesis require no such conditions, and each chapter sees the maintainence of regioselectivity towards the branched product in ionic liquid, isopropanol and ethylene glycol. The simple change of solvent from ionic liquid to ethylene glycol allows a dramtic decrease in reaction times also.

Chapter five uses low catalyst loadings in ethylene glycol in a simple catalyst system using high substrate/catalyst ratios which have never before been seen for this type of coupling reaction, producing completely selective branched products at high yields.

CHAPTER ONE

Introduction

1.1. A Brief History Through Catalysis

Catalysis is of paramount importance in the chemical industry as it is the key to the efficiency of chemical conversions especially in an age of increasingly limited energy and non-renewable resources, alongside mounting concern for the environment. It is estimated that approximately 90% of all chemical products produced for commercial applications involve catalysts at some stage in the process of their manufacture, and the production of most industrially important chemicals involve catalysis.[1,2] Catalytic reactions, rather than stoichiometric, are preferred and are associated with environmentally friendly green chemistry due to the reduced amount of waste generated.[3] It is a rather daunting task to open with such a vast and growing subject matter; however it seems quite apt to start at the known beginnings of catalysis.

Soluble (homogeneous) and heterogeneous catalysis was implemented by the chemical industry after 1910.[4] Whilst heterogeneous catalysis grew steadily, the use of soluble catalysts was minor until the 1950s, mainly because large scale hydrogenation reactions were found to proceed well with solid catalysts (Figure 1.01). These reactions included the synthesis of methanol and ammonia. The applications of homogeneous catalysis were largely limited to reactions of acetylene, an expensive starting material, manufactured principally from raw materials of calcium carbonate and coal. In spite of its cost, however, acetylene was used to produce many organic chemicals, such as acetaldehyde, acrylonitrile, and vinyl monomers. In the Kucherov reaction (invented in 1881 by the Russian chemist Mikhail Kucherov) acetylene is

hydrated to acetaldehyde with a mercury salt such as mercury(II) bromide.[5] Before the advent of the Wacker process this reaction was conducted on an industrial scale.[6] Walter Reppe discovered that acetylene can react at high pressures with heavy metal catalysts to give industrially significant chemicals.[7] Acetylene reacting with alcohols, hydrogen chloride, or carboxylic acids to give vinyl compounds, or with hydrogen cyanide to yield acrylonitrile. Above 400 °C (673 K) the pyrolysis of acetylene will start, which is relatively low for a hydrocarbon.[8] The main products are the dimer vinylacetylene (C_4H_4) and benzene.

The period between 1950 and 1980 saw the advancement of innovative chemistry in terms of development and chemical science, which encompassed an explosion in the knowledge of organometallic chemistry, and its use in catalytic processes. Nobel prizes were awarded to Karl Ziegler, Giulio Natta, Geoffrey Wilkinson, and E. H. Fischer for their contributions to this part of science and technology, which incorporated a new area of organometallic catalysis. Figure 1.01 illustrates how the volume and value of commodities have increased with time, with a particularly dramatic growth in the 1950's. The value of products derived from organometallic catalysis and homogeneous catalysts are equally as impressive as its heterogeneous counterparts.[4]

After World War II, catalysis underwent a growth spurt at a time of great technological advancement. The impressive performance of high octane gasoline in aircraft engines was a result of cracking in heterogeneous catalysis.[9] The Fischer-Tropsch process saw the production of "synthetic gas", where a mixture of CO and hydrogen was reacted over a metallic catalyst, producing a gaseous mixture of hydrocarbons not dissimilar to fuel oil, processes that are still very much in existence.[10,11] Alongside the growing use of automobiles, a greater demand for high

quality gasoline promoted an incentive to broaden the use of catalytic cracking into a more efficient process and refine the reforming techniques for petroleum.[4]

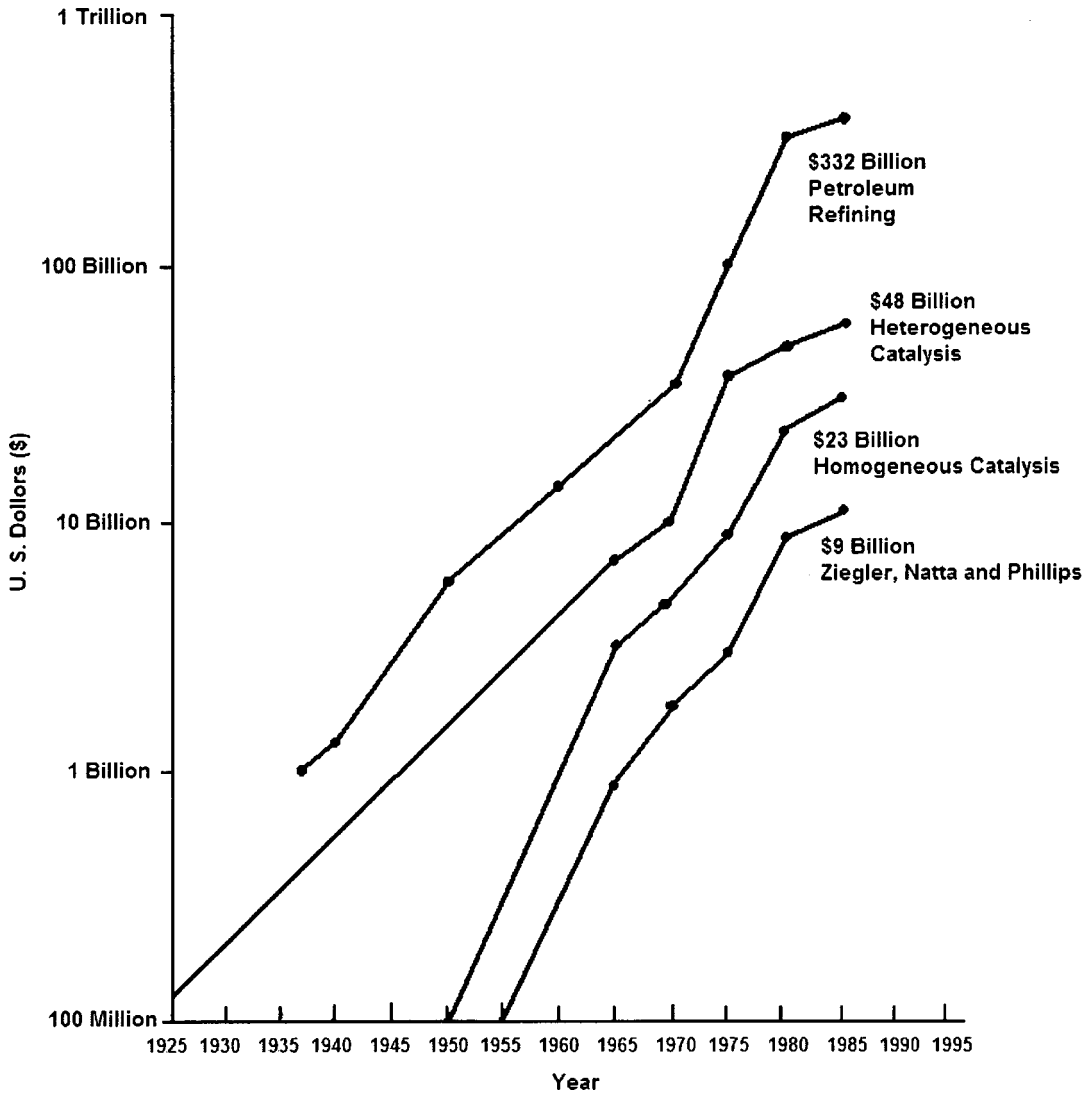


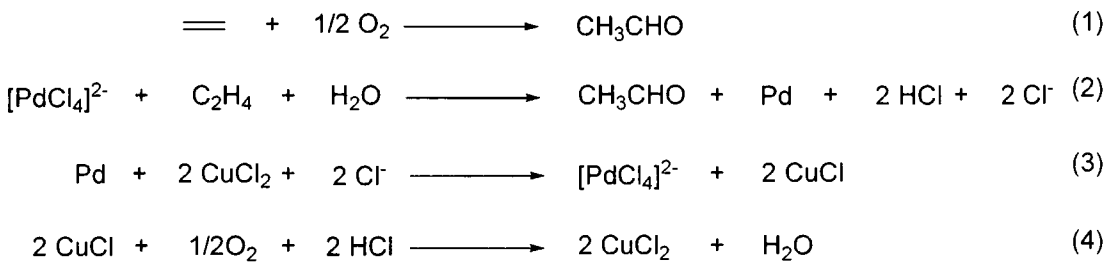
Figure 1.01. The growth of catalysis in the 20th Century.[4]

In the same way the growth of other industries, such as the synthetic polymer industry, created a demand for new, highly pure chemical intermediates favouring the use of soluble catalysts. Soluble catalysis was found to provide a higher selectivity towards the formation of a single product, which was the key advantage over heterogeneous catalysis.

A technological evolution was looming, alongside a market pull for new chemical processes. Such a process was developed by Ziegler and coworkers, who documented the use of titanium based catalysts to prepare polyolefins.[12] Natta then used similar catalysts to polymerise terminal alkenes, and their individual projects lead to the development of the Ziegler-Natta catalyst based on titanium and organometallic aluminium compounds, for example triethylaluminium, $Al(C_2H_5)_3$.[12] The Ziegler-Natta catalyst represented a major breakthrough in polymerisation chemistry due to its ability to produce a variety of commercially important polymers with high stereoselectivity, and represents the first examples of achieving selective products with metal catalysts. In 1963 Natta and Ziegler both won a Nobel Prize in Chemistry for their work on high polymers. The discovery saw the birth of one of the major industries, the production of thermostatic polyolefins, and the Ziegler-Natta catalyst is still used to mass produce polyethylene and polypropylene.[13] Polyethylene is a commodity thermoplastic heavily used in consumer products (over 60 million tons are produced worldwide every year).[14]

Zeise discovered that platinum group metals could coordinate to ethylene to form stable Pt complexes, now known as Zeise's salt ($K[PtCl_2(C_2H_4)]$), and is one of the first organometallic compounds to be reported.[15] In 1894 an American chemist Phillips discovered that palladium (II) chloride analogues could reduce to palladium metal when in contact with ethylene.[16] The product of this process was acetaldehyde. Even in substoichiometric amounts, palladium salts were far too expensive to be used as an oxidising agent, so the process failed to have any sort of immediate technological impact. Nevertheless, this reaction is considered to be the starting point of homogeneous catalysis. Chemists at Wacker-Chemie discovered that this reaction could be made catalytic after reoxidising the palladium species in air, and paved the

way for the reaction we now know as the Wacker process.[12] This marked the beginning of an era for the production of chemicals from petroleum feed-stock and is one of the first examples of homogeneous catalysis.[17,18] The Wacker process flourished in industry as it replaced the expensive starting material acetylene with cheaper ethylene (Eq. 1-4).



The overall reaction is given in Eq. 1, where only the alkene and oxygen are consumed and the catalysts are regenerated (Eq. 2). Without copper(II) chloride and hydrochloric acid acting as oxidising agents, the Pd(0) resulting from reductive elimination of Pd(II) would precipitate out and the reaction would come to a halt (without catalyst regeneration the stoichiometric reaction occurs) (Eq. 3). Air, pure oxygen, or a number of other oxidisers can oxidise the resultant CuCl back to $CuCl_2$, allowing the cycle to repeat (Eq. 4).[12]

Different catalysts can perform diverse transformations on the same functional group; in the absence of the catalyst the reaction may not proceed, proceed slowly, or progress in an unselective manner. Such processes are eminent within organic synthesis, for instance, the Monsanto process,[19] olefin metathesis using Grubbs' catalyst,[20] the Heck reaction,[21] and the aforementioned Wacker process and many more.

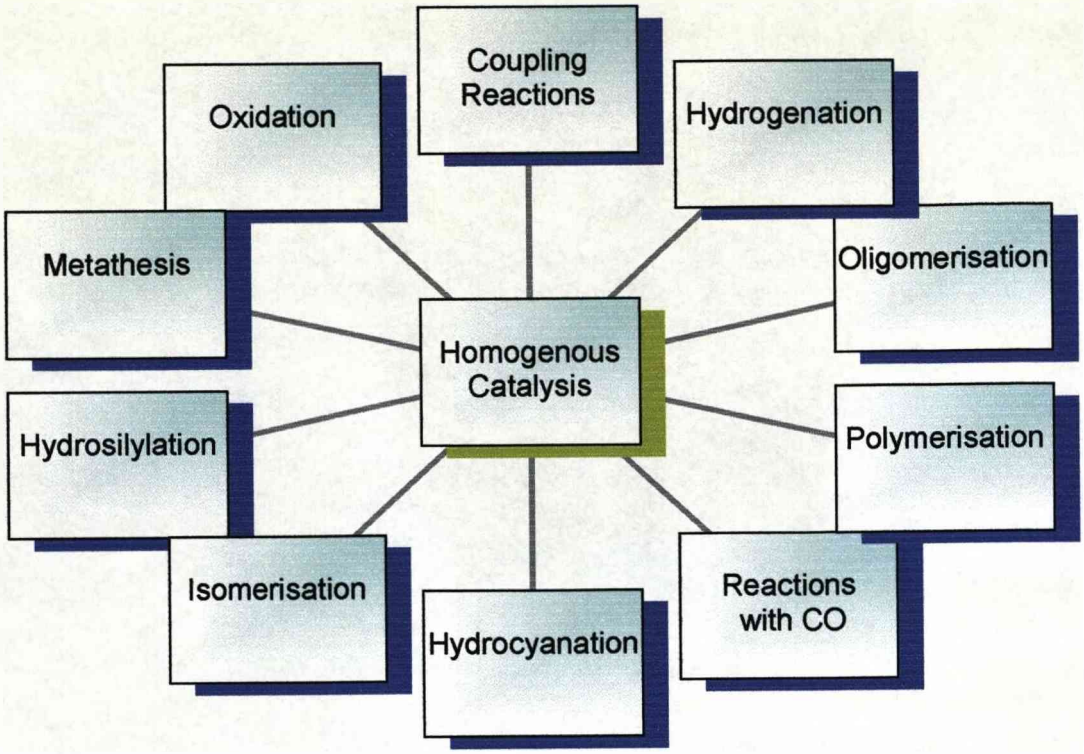


Figure 1.02. Reactions catalysed by transition metal catalysts.

High activity and selectivity are now associated with homogenous catalysis, where step changes of applications in technology have been accompanied by development in organometallic chemistry. The production of commodity chemicals has dominated homogeneous catalysis, but the balance is now slowly shifting towards fine chemical manufacture, where high selectivities are paramount. Figure 1.02 displays the vast range of transformations encompassing homogenous catalysis.

A number of transformations exist where there is no heterogeneous counterpart, thus unique to homogenous catalysis. A few examples include the hydrocyanation of butadiene to adiponitrile, conversion of CO/H_2 to ethylene glycol, and also an increasing number of enantioselective hydrogenation and oxidation reactions. Homogeneous catalysis is the subject of this thesis.

1.2. Green Chemistry and Catalysis

A worldwide demand for novel and cost-effective approaches to pollution prevention provides an incentive for more environmentally friendly chemical processes and products. One of the most attractive concepts for pollution prevention is green chemistry, which is best defined as *the utilisation of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products.*[22,23] Significant progress is being made in several key research areas such as catalysis, the design of safer chemicals and environmentally benign solvents, and the development of renewable feed stocks. It is important to note that the rapid development of green chemistry is due to the recognition that environmentally friendly products and processes will be economical in the long term; so current and future chemists are being trained to design products and processes with an increased awareness for environmental impact.[24]

The area of catalysis is sometimes referred to as a "foundational pillar" of green chemistry.[25] Catalytic reactions can reduce energy requirements and decrease separations due to increased selectivity.[26-29] Stoichimetric amounts of reagents may also be permitted in certain circumstances; but minimising the quantities is essential if starting materials are expensive or difficult to obtain. There is no doubt that the 2001 Nobel Prize-winning work of Sharpless,[30] Noyori,[31] and Knowles[32] meet many green chemistry goals.[33,34] Pioneering research on catalytic asymmetric synthesis has been vital in producing single enantiomer compounds which are of fundamental importance to the pharmaceutical industry.[35]

It was Curzons and coworkers who stated that rigorous management of solvent is likely to result in the greatest improvement into making processes "greener." [36] Traditionally, catalytic processes have employed organic solvents as reaction media,

which can have their associated risks due to their flammability, toxicity and volatility, posing a great deal of safety, health and environmental issues. Many are classified as volatile organic compounds (VOCs), hazardous air pollutants (HAPs) and/or carcinogenic. The phasing out of many organic solvents is becoming a matter of concern, and novel alternatives are constantly being sought. Targeting solvent use in the quest for more benign synthesis seems apt, because they are used in large quantities as either reaction media, or in the extraction of products. The last decade has seen the design of "greener" solvents and solventless systems, which has grown to become a very active area of green chemistry.

1.3. Novel Reaction Media

In recent years, many strides have been taken to find adequate replacements of traditionally used solvents for organic reactions, which fulfil the criteria for a sustainable chemical process. Those that are on the "solvent blacklist" include chlorinated hydrocarbons (DCM), benzene, acetonitrile, DMF, DMA and hexane to name but a few.[37]

With much of the attention focussed on circumventing the need for volatile solvents, more research would allow an opportunity to vastly improve and extend the *role* of solvent to facilitate catalyst recycle and recovery, thus rectifying a key factor which has impeded the application of homogenous catalysis over its heterogeneous counterpart. The ideal choice of solvent should be relatively non-toxic or non-hazardous. The issues surrounding the use of volatile or toxic solvents have prompted fine chemical and pharmaceutical industries to find alternative media. The best choice of solvent of course would be no solvent, or water, but in most cases this is not possible due to solubility issues. Generally, lower alcohols are preferred, for example,

the natural product ethanol which is biodegradable.[38,39] Other factors associated with solvent is their containment, recovery and ability to be recycled. Homogenous catalysis often involves cumbersome routines in terms of separation, and the isolation of product from a still active catalyst can prove quite complex. Therefore, the challenge is to adhere to the good features of homogenous catalysis without compromising selectivity and activity, but support other aspects that have hindered its widespread use in industry. [26]

Receiving significant attention over recent years in terms of unconventional solvent media has been water, supercritical CO_2, fluorous carbons and ionic liquids. Water would be the ideal choice, it is the most abundant, natural and non-toxic solvent on earth. Breslow's report on the acceleration of Diels–Alder reactions in aqueous media led chemists to re-examine water for use as a solvent for chemical applications.[40] With proper design of catalyst and reaction conditions, water has now exploded onto the chemistry scene with a vengeance.[41-43]

From the initial research of supercritical fluids in academic laboratories, to its use in commercial processes today, one sees an excellent example of how frontier research can evolve and suit the current needs in terms of green processes.[44-51] Supercritical CO_2 is receiving considerable attention for its easy recycle, non-toxicity, non-flammability and tunability (in the supercritical state, the physiochemical properties of the solvent can be tuned by changing its density). Benefits also include a potential to combine reaction and separation processes and the solubility of organic compounds is met with ease. However, it proves to be a poor solvent for inorganic salts; a careful choice of counter ion can greatly increase the solubility of charged complexes. Anions such as trifluoromethyl sulfonate tetrakis(3,5-bis(trifluoromethyl)phenyl)borate, (BARF),[52,53] and cations such as

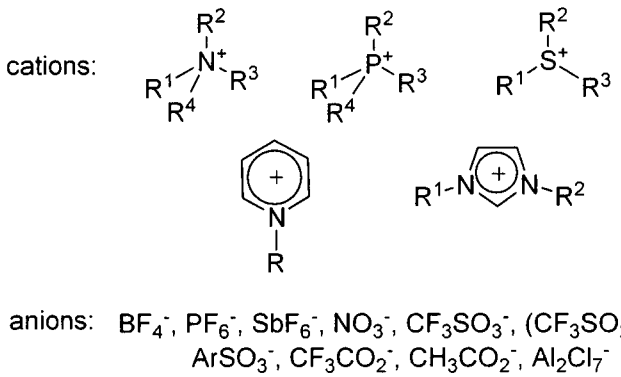
fluorotetraalkylammonium and morpholinium[54] have been shown to increase solubility.[48,55] Another approach to increase the solubility of catalysts in supercritical fluids entails attaching long perfluoroalkyl groups to phophine ligands. Phosphine ligands with $-CF_3$, (sometimes $-C_6F_5$) groups were attached to catalyst in order to increase solubility in $scCO_2$.[56-58] Supercritical CO_2 is to some degree similar to fluorinated liquids. Fluorous solvents have low dielectric constants, low toxicity, and high chemical and thermal stability.[59-61] They exhibit properties dissimilar to most common organic solvents, but allow good miscibility at higher rather then at lower temperatures, making them an ideal choice for homogenous or bi/triphasic catalysis.[62,63]

Currently, the "official" definition of ionic liquids uses the boiling point of water as a point of reference: "Ionic liquids are ionic compounds which are liquid below 100 °C." More commonly, ionic liquids have melting points below room temperature; some of them even have melting points below 0 °C. [64]

Compared with supercritical CO_2 and fluorous solvents, ionic liquids sit on the opposite side of the solvent spectrum. Since ionic liquid form a major part of this thesis, a more detailed description is provided below.

Ionic liquids, also referred to as molten salts, can be described as liquids composed solely of ions, and remain liquid at or below room temperature. The strong ionic (Coulomb-) interaction within these substances results in a negligible vapour pressure (unless decomposition occurs), a non-flammable substance, and a high thermally, mechanically as well as electrochemically stable product. These points make ionic liquids highly attractive for use as solvent as they are also easy to manage. The composition of a typical ionic liquid comprises a large, bulky cation, and a smaller anion (Scheme 1.01).

The choice of the cation has a strong impact on the properties of the ionic liquid and will often define the stability. The chemistry and functionality of the ionic liquid is, in general, controlled by the choice of the anion. The combination of a broad variety of cations and anions leads to a theoretically possible number of 10^8 ionic liquids. However, a realistic number will be magnitudes lower. Today about 1000 ionic liquids are described in the literature, and approximately 300 are commercially available.[64] Typical structures combine organic cations with inorganic or organic anions: The cation is usually unsymmetrical in order to be a liquid at room temperature, where, for example, R^1 and R^2 are different alkyl groups in the dialkylimidazolium cations.[65]



Scheme 1.01. Typical structures of ionic liquids.

Ionic liquids have existed for many years and were first documented by Walden in 1914,[66] but with latter day technologies available, research into the use of ionic liquids based on chloroaluminate anions ($AlCl_4^-$ or $Al_2Cl_7^-$) by the groups of Fannin,[67,68] Mamantov,[69] and Osteryou[70,71] allowed the field to flourish. The modern day dialkylimidazolium based ionic liquids were only reported in the 1980s by Wilkes and coworkers.[72,73] Even though ionic liquids were a promising solvent for Friedel–Crafts acylations,[74] the chloroaluminate anion's affinity for water inhibited the widespread

use of this ionic liquid as solvent. Wilkes and coworkers then went onto to synthesise a range of ionic liquid salts containing the dialkylimidazolium cations, and work by his group and others illustrated that different combinations of cation/anion allowed the solvent properties to be "tuned".[73,75] For example, the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) is miscible with water, but if the anion is replaced by PF_6, it is immiscible, and both are stable towards hydrolysis. Properties such as lipophilicity can also be changed according to the size of alkyl chain on the imidazolium cation. This tunability element is why ionic liquids have received significant attention as an alternative to conventionally used organic solvents, alongside a number of other advantage points:[65]

- They have reasonable thermal stability. Water has a liquid range of 100 °C; whereas ionic liquids have liquid ranges of more than 300 °C.
- They have an ability to dissolve a wide range of organic, inorganic and organometallic compounds.
- They have essentially no vapour pressure; they do not evaporate easily and are easy to contain.
- They are able to form two/three-phase systems with some organic solvents, allowing easy catalyst/product separation, *e.g.* [bmim][PF_6] is known to readily form a triphasic system with water and non-polar solvents (Fig 1.03).

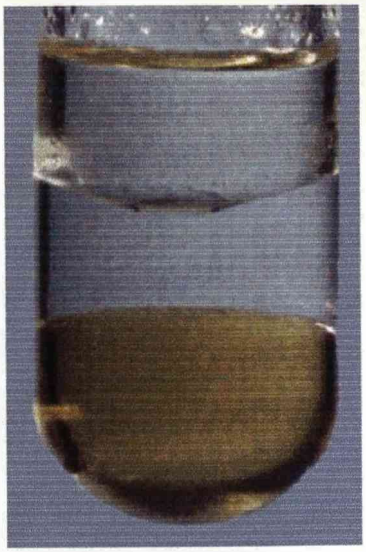


Figure 1.03. A tri-phasic system allowed by ionic liquids (bottom phase: ionic liquid; middle phase: water; top phase: diethyl ether).

- They are attractive solvents for numerous reactions, for example, in catalytic hydrogenations, carbonylations, hydroformylations, and aerobic oxidations, as the solubility of gases such as H_2, CO and O_2 is generally good.[76]
- Lipophilic ionic liquids can be used in aqueous biphasic systems.
- Polarity and hydrophilicity/lipophilicity can be readily adjusted by a suitable choice of cation/anion (Scheme 1.01) and so ionic liquids have been referred to as "designer solvents".
- They are often composed of weakly coordinating anions, hence, having the potential to be highly polar yet non-coordinating solvents.
- They can be expected to have a strong rate-enhancing effect on reactions involving cationic intermediates.

The points listed above suggest that the use of ionic liquids as reaction media can confer many advantages upon catalytic reactions over organic solvents. In ionic liquids, catalysts having polar or ionic character can be easily immobilised without additional structural modification and the ionic solutions containing the catalyst can easily be separated from the reagents and reaction products, and then can be reused. Switching from an organic solvent to an ionic liquid can result in a significant improvement in catalytic performance, *e.g.*, rate acceleration, improvement of (enantio)selectivity and an increase in catalyst stability. [77]

An ionic liquid, in the form of tetraethylammonium trichlorostannate, was first introduced to homogeneous catalysis in the platinum catalysed hydroformylation of ethene, described by Parshall in 1972, the importance of which was not noticed till the early 1990s.[78] Ionic liquids then came into prominence largely due to the pioneering works of Seddon,[79,80] and Chauvin[81] and recently the studies of Welton[82] and Keim and Wasserscheid.[83] The late 1990s earned ionic liquid a reputation as an exceptional and novel alternative to molecular solvents for catalytic hydrogenations,[84-86] hydroformylations,[81,87,88] isomerisations,[81,89] olefin dimerisations,[90-92] oligomerisations[93] and polymerisations[94,95] and Heck couplings,[96-101] with an ever-expanding scope. The palladium-catalysed Heck coupling has been studied for nearly a decade in the Xiao group, and forms the theme of this thesis.[102-111]

Ionic liquid can also have potential disadvantages. They can be expensive in comparison with molecular solvents, and can take days to synthesise in the laboratory to an effective purity. Ionic liquids are safer solvents compared to standard organic solvents because they are non-flammable, have low vapour pressure at room temperature and can be recycled. They can be viscous, and be poorly biodegradable

and the major concerns are the unknown toxicity of ionic liquids to humans and the environment.

1.4. Palladium

Palladium is a rare and precious metal in the family of Platinum Group Metals (PGMs) together with platinum, rhodium, osmium, ruthenium and iridium. They are given this general classification as they share similar physical and chemical properties. PGMs are able to withstand oxidation and corrosion so are often quite aptly termed the noble metals.

The high melting points of PGMs originally hindered their use in industrial applications, until the development of new refining methods. Palladium was discovered in 1803 by W. H. Wollaston, a British chemist, and his initial techniques in the separation of PGMs are still considered to be the basis for modern PGMs metallurgy.[112-116] In 1828, just one month before his death, Wollaston described the method by which he rendered platinum malleable and, in a final section, he described his method of making malleable palladium. This involved heating $Pd(CN)_2$ with sulfur, followed by cupellation in an open crucible with nitre and borax; the residue was subjected to a low red heat whereupon a malleable ingot of palladium metal resulted.[117]

The superior chemical and physical properties of palladium make it one of the major metals under the PGMs, and its application has grown considerably since the 1970s. Industrial applications have monopolised palladium the most, particularly in "green" applications, for example, for use as an autocatalyst replacing less efficient platinum in the automobile industry. The second largest demand sector for palladium is jewellery, closely followed by electronics (Figure 1.04).

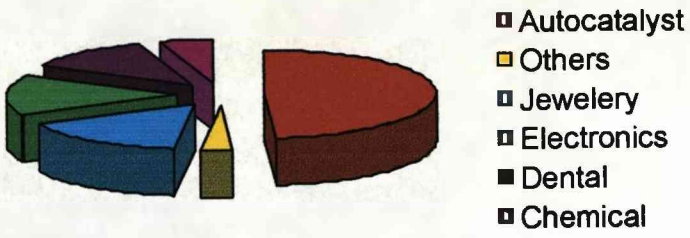


Figure 1.04. Pie chart representing the demand for palladium in 2007.[118]

After the ore is extracted (usually obtaining 7g Pd/ton), the ore enters the crushing/grinding stages, to liberate the sulfide minerals from the gangue minerals. This is done in several steps to optimise the grinding efficiency without jeopardising overall recovery of the Pd and Pt containing sulfide minerals. Crushers are used as the first stage of size reduction followed by grinding mills which contain steel grinding balls used to induce energy and breakage of the ore. After the grinding stage, flotation reagents are added to aid separation of Pd and Pt sulphide minerals from the gangue material, consisting of collectors (potassium amyl xanthate) and depressants (carboxymethylcellulose). The collectors adsorb on the surface of the sulfide minerals and render them hydrophobic (water resistant) while the depressant adsorbs on the surface of the gangue mineral talc rendering it hydrophilic (water affinitive). These flotation reagents are then allowed to condition for a limited amount of time prior to the flotation step.[119]

Following optimum grinding and reagent addition, the slurry is exposed to the flotation process. In this process the slurry is agitated while air is induced into the system. This air naturally attaches to the now hydrophobic sulfide particles and causes them to float to the top of the slurry level forming a froth layer. This froth layer is then collected as concentrate and subjected to further "cleaning" flotation steps which

continue to separate the sulfide minerals from the remaining gangue minerals. After the ore has been extracted from the ground, and has been crushed, milled, and concentrated, it is transported to a smelting facility as a high-grade PGM filter cake, and entered into an electric furnace, where it is heated at temperatures ranging from 1300-1600 °C. As the concentrated ore melts, two liquid phases form: a denser molten matte (rich in nickel and copper sulphides as well as other base and precious metals) and a lighter silicate and iron rich slag. The sulphide minerals form a matte that is treated further; the oxide and silicate minerals (referred to collectively as "gangue") are discarded as slag, usually after being subjected to granulation using a high-flow water stream, milling, and flotation to re-capture any additional desired minerals.[119]

Furnace matte, consisting of a combination of base metals (nickel, copper, cobalt, iron, and sulphur) and the desired PGMs, is tapped periodically in preparation for converting, the process by which air is blown into the molten matte over a period of several hours to remove the majority of the iron and sulphur content through oxidation. [119]

The refining process is indeed the most complex and time-intensive aspect of PGM recovery. As a result, mining companies continue to devote a considerable amount of their capital resources to developing new, and presumably better PGM refining technologies. While the major mining companies go to great lengths to protect their proprietary refining methods, the basic parts of the process remain fairly consistent throughout the industry.[119]

The obvious goal of the refining process is to further separate minerals containing platinum group metals from base metals and other impurities to obtain the highest-grade PGM filter cake possible. Though the process becomes incredibly detailed, it

can be condensed into three main activities: pressure leaching, solvent extraction, and PGM precipitation.

However, the refining process does not adhere to a strict linear progression in the way that some of the preceding steps do. Rather, it involves a set of discrete circuits designed to isolate different metals. The concentration and smelting of PGM-rich ore produces a successively higher-grade filter-cake that lends itself to the series of intricate chemical processes carried out during the refining phase.

The enriched converter matte received from the smelter is subjected to a batch grinding process in a closed ball mill, producing a heated slurry, that is then cooled and stored in a surge tank before it is conveyed to a series of autoclave leach circuits, each designed to precipitate a particular metal from the solution through pressure oxidation.

Pressure oxidation, the process of conducting chemical reactions under high pressure and temperature, can take a variety of forms. Most mining companies, however, rely on the high solubility of PGMs like palladium and platinum (as well as gold) in aqua regia, a mixture of hydrochloric and nitric acids.

Aqua regia leaching dissolves platinum, palladium, and gold minerals and leaves other PGM and base metal components as solids in the leach residue. After the gold is segregated from the solution through a process called solvent extraction, the remaining solution is treated with ammonium chloride to precipitate the platinum as ammonium chloroplatinate. The crude platinum salt that results is then heated to create a fine platinum powder. It is then re-dissolved in this form in aqua regia, precipitated once more with ammonium chloride, and calcined to pure metal.

The palladium, still left in solution, is precipitated with ammonia. The crude palladium salt produced by the addition of ammonia is recovered through filtration,

re-dissolved in ammonia, and precipitated to form high-grade palladium salt. This powder is usually converted to metallic form through chemical reduction involving formic acid.

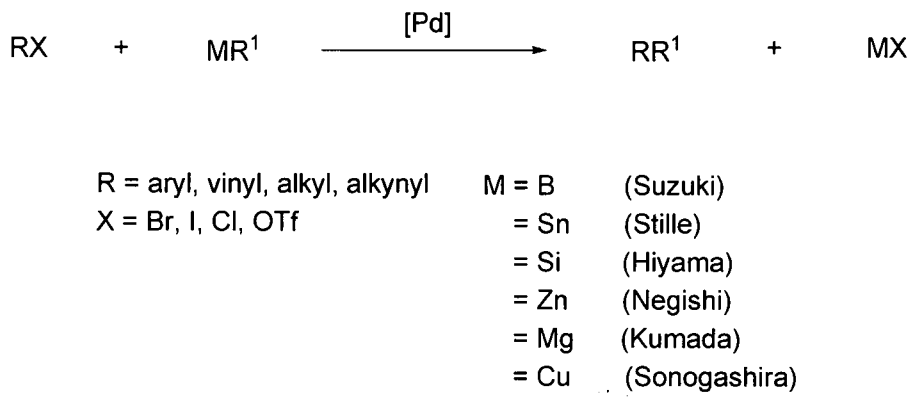
The rising cost of palladium has resulted in a steady decline in demand by industry. This is attributed to a number of reasons. Improved efficient emission systems were devised allowing lower catalyst loadings, alongside an increase in autocatalyst recovery. The electronics industry mainly use silver-palladium alloys in multi-layer ceramic capacitors (MLCC) which find use in mobile telephones, laptop and standalone computers, fax machines and in auto and home electronics. However, the cost of Pd alongside a more advanced knowledge on electronic technologies has driven the industry to apply cheaper base metals such as nickel as an alternative conductor within the MLCC.[120]

In terms of chemical applications, palladium has found place in the armoury of synthetic chemists for its catalytic performance in a wide variety of reactions and transformations ranging from hydrogenation, dehydrogenation, hydrogenolysis reactions to oxidation (Fig. 1.02). The first reaction to showcase the potential of palladium was the Wacker process commercialised in the 1960s (*vide supra*).

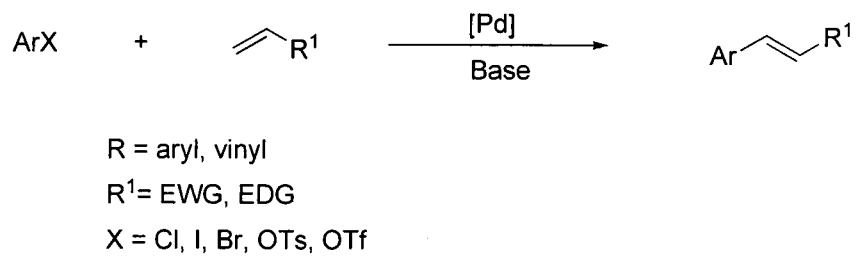
1.5. Palladium Catalysed Cross-Coupling Reactions

Palladium catalysis is now considered to be an indispensable tool for organic and inorganic synthesis. Transition-metal catalysed carbon–carbon bond formation was developed in the 1970s, and represents a milestone in synthetic organic chemistry, allowing the cross-coupling of substrates in ways that were previously thought impossible.[121,122] The popularity of cross-coupling reactions is attributed to their tolerance for many functional groups, allowing the construction of complex

molecules. These reactions include Suzuki,[123,124] Stille,[125,126] Hiyama,[127] Negishi,[128] Kumada,[129] Sonogashira[130,131] couplings and finally, the Heck reaction. The palladium-catalysed cross-couplings of aryl and vinyl halides/triflates with organometallic reagents serves as a straightforward method for formation of carbon-carbon bonds (Scheme 1.02), whereas the Heck reaction couples aryl halides with an olefin (Scheme 1.03).



Scheme 1.02. Palladium catalysed cross-coupling reactions.



Scheme 1.03. The Heck reaction.

Scheme 1.02 and 1.03 illustrate palladium's versatility for a range of reactions in which the organometallic reagent containing the R^1 group can be saturated or

unsaturated (for example, alkyl, aryl, vinyl, and alkynyl). Transmetallation occurs most easily for magnesium, tin, and zinc reagents with the aid of palladium, and circumvents the requirement of an additive. Boron and silicon reagents are usually more reluctant to transmetallate in the absence of some activator. Typically Suzuki and Hiyama cross-couplings are carried out in the presence of an additive, the role of which is to form a higher valent, more reactive "ate" complex.[122]

There are many articles and reviews covering each subject, but it is beyond the scope of this thesis to thoroughly examine each reaction, an arduous task which would entail many volumes![123-131] The main subject of this thesis will be the Heck reaction which has acquired a special place due to its versatility and wide scope.

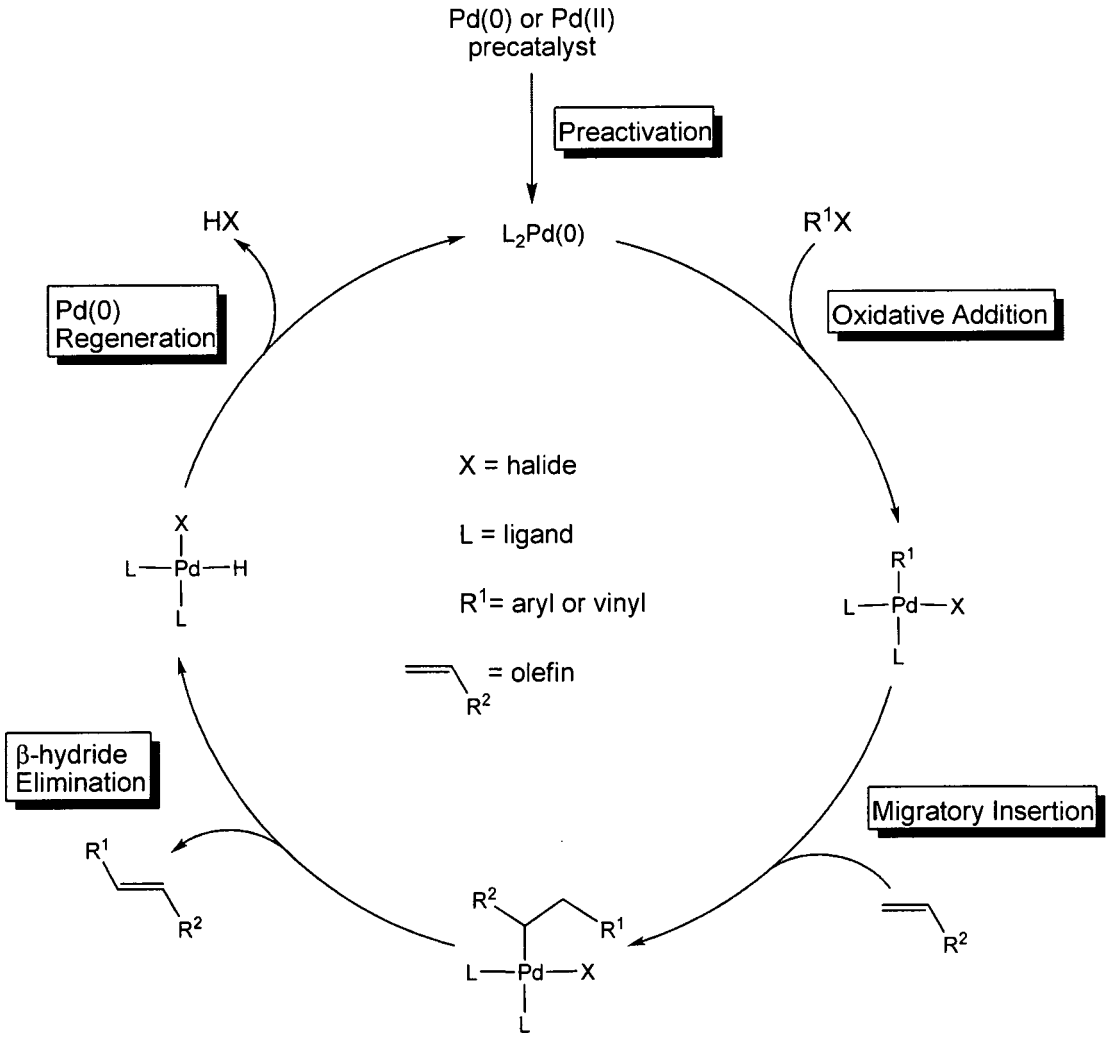
1.6. The Heck Reaction

The Heck reaction has been a reaction of great importance and intrigue since its conception in the late 1960s. Heck demonstrated that organopalladium salts undergo various vinylic substitution reactions, stemming from research carried out on the transmetallation of organomercury compounds.[132-139] The reaction, sometimes referred to as the Mizoroki-Heck reaction, was discovered independently by Richard Heck[140] and Tsutomu Mizoroki[141] in 1971-1972, and was developed further by Heck and coworkers, who found that the reaction could tolerate a wide range of substrate functionalities (Scheme 1.03).[142-147] The classical reaction involves the formation of a carbon-carbon bond between two sp^2 carbon centres by the overall substitution of a C-H bond of an alkene by an aryl or vinyl group, under basic conditions. The boundary of scope is not yet defined: substrates that were considered *unheckable* are being fractured with yet another improvement.[21,121,122,148-153] There are numerous reviews and articles on Heck chemistry, and before venturing into this subject, it is important

to discuss some of the aspects associated with Heck chemistry to gain a better understanding on the immense topic, even though it is merely the tip of the iceberg in terms of what has been documented.[21,152-155]

1.6.1. The Heck catalytic Cycle

Scheme 1.04 gives a simplified view (termed "simple" as no single schematic could reflect the complexity of all relevant steps of Heck Chemistry) of the major steps in the Heck catalytic cycle.[156]

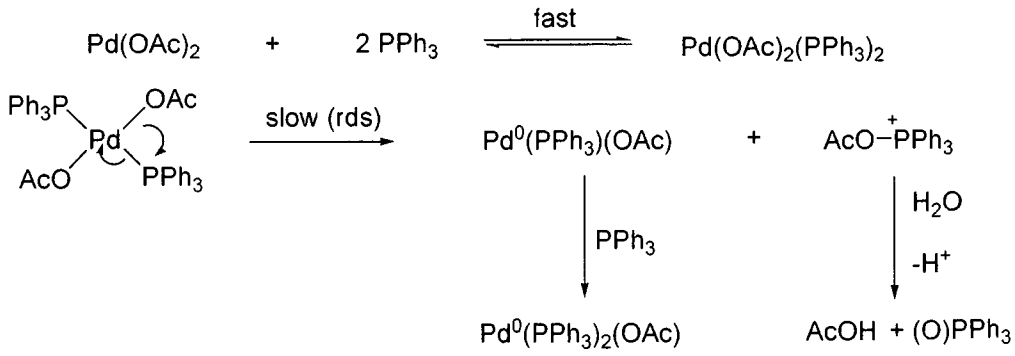


Scheme 1.04. The Heck catalytic cycle.

The pre-activation step, often omitted from depictions of the Heck catalytic cycle, starts the whole process where a palladium(0) complex or palladium(II) salt is transformed into the generally assumed, catalytically active 14-electron Pd(0) complex. The Pd(0) complex then undergoes an oxidative addition step with R-X to from the Pd(II) complex. Then, a ligand or halide dissociates, leaving an empty co-ordination site where the complex undergoes π–coordination with the adjoining olefin, in order for migratory insertion then to occur. This step is essentially the product forming step, where the carbon-carbon bond is constructed. The β-hydride elimination results in the coupling product and a hydrido Pd(II) complex, where a base is required for the prompt removal of HX to regenerate the Pd(0) complex, thus completing the full cycle.

1.6.2. Preactivation Step

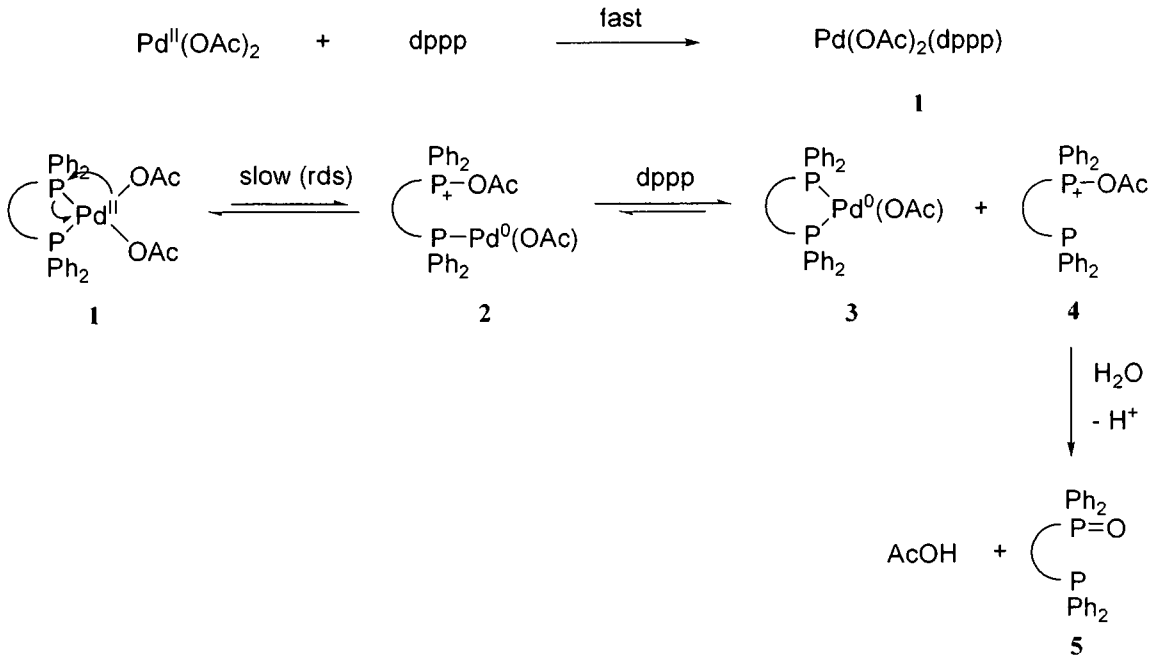
The reactive 14-electron species is formed from the preactivation of the precatalyst, which can be either Pd(0) or Pd(II). This step has been extensively studied by Amatore and Jutand,[157-161] and they established that a Pd(0) complex is formed spontaneously from $Pd(OAc)_2$ and monodenatate phosphines in an irreversible intramolecular reduction of Pd(II) by the phosphine.[162-164] Phosphine oxide is formed in the reduction process, which is irreversible (Scheme 1.05).[165] Hard nucleophiles assist this reduction, *e.g.* hydroxide and alkoxide ions, water, and acetate ion. [21]



Scheme 1.05. Mechansim of the formation of Pd(0) from $Pd(OAc)_2$ and PPh_3.

In 2001, Amatore and coworkers proposed that, in the presence of two equivalents of a bidentante ligand, for example, 1,3-bis(diphenylphosphino)propane (DPPP), a hemioxide DPPP(O) **5** is formed (Scheme 1.06). Initially, a slow intramolecular reduction step occurs (**1**→**2**), followed by a reversible, fast ligand substitution on Pd(0) (**2**→**3**), and the final step is the hydrolysis of the phosphonium salt **4**, thus producing the hemioxide DPPP(O) **5**. DPPP effectively acts as a reducing agent, consequently forming the anionic Pd(0) complex **3** which is thought to be the active complex taking part in oxidative addition.[165]

Even though the Heck reaction can proceed without the need for ligand (*i.e.* just $PdCl_2$, $Pd(OAc)_2$), the efficiency of the reaction can be improved with the addition of particular ligands. Ligands can be seen as stabilising the palladium species in the catalyst, avoiding premature degradation.[155] Finding the perfect ligand for a reaction is often the result of chance, trial and error, rather then a matter of predicting the most efficient.[21]



Scheme 1.06. Mechanism for the formation of Pd(0)-dppp.

1.6.3. Oxidative Addition

Oxidative addition may involve a concerted process where the dissociation of the C-X bond of the aryl halide is synchronised with the formation of the Pd-X and importantly, the Pd-C bond, but is still under scrutiny.[21,166] This stage is much less sensitive to the substituents of the unsaturated system, but more to the nature of X, where order of reactivity follows the order Ar-I ≥ Ar-OTf ≥ Ar-Br ≥ Ar-Cl,[162] corresponding to the experimentally found bond dissociation energies of 96 (Ar-Cl), 81 (Ar-Br) and 65 (Ar-I) kcal/mol, repectively.[167] Oxidative addition onto the generally assumed active 14-electron species generates *cis*-RPdXL$_2$ which isomerises to the thermodynamically more stable *trans* configuration. A free coordination site is necessary for the alkene to insert, created through the delegation of a ligand or halide. The oxidative addition step is frequently considered to be the rate determining step, especially in the case of a strong C-X bond (*e.g.* C-Cl).

Electron-donating substituents on the aryl group make oxidative addition more cumbersome (-OCH_3, -CH_3, *etc.*). Because of this, electron-rich aryl halides are referred to as "deactivated", and electron-poor aryl halides are regarded as "activated". In the earlier years, attention had mostly focussed on aryl iodides due to the ease of reaction; aryl chlorides had enjoyed less of the limelight. However there are added benefits in expanding the substrate scope to aryl bromides and chlorides, which has attracted considerable interest over recent years. In terms of availability, iodides are less desirable then their chloride/bromide counterparts and are also more expensive. There are many chloride and bromide aryls available. Organic iodides can only take part in reactions at mild temperatures, which can offer a disadvantages in terms of activation energy.

1.6.4. Migratory Insertion

Migratory insertion is the product forming step of the Heck cycle. The importance of this step can be realised as being responsible for the stereo- and regioselectivity of the product. There are three possibilities as to why this may be the case:

1) RPdX behaves as a carbanion. Insertion undergoes a nucleophilic addition, a reaction similar to nucleophillic substitution found with vinylic compounds. Evidence for this is based on the high reactivity of Michael acceptors (*e.g.* acrylates, acrylonitrile) in the Heck reaction.[168]

2) the olefinic bond undergoes a typical electrophilic addition by RPdX or RPd^+ which act as metal-centred electrophilic intermediates.[21]

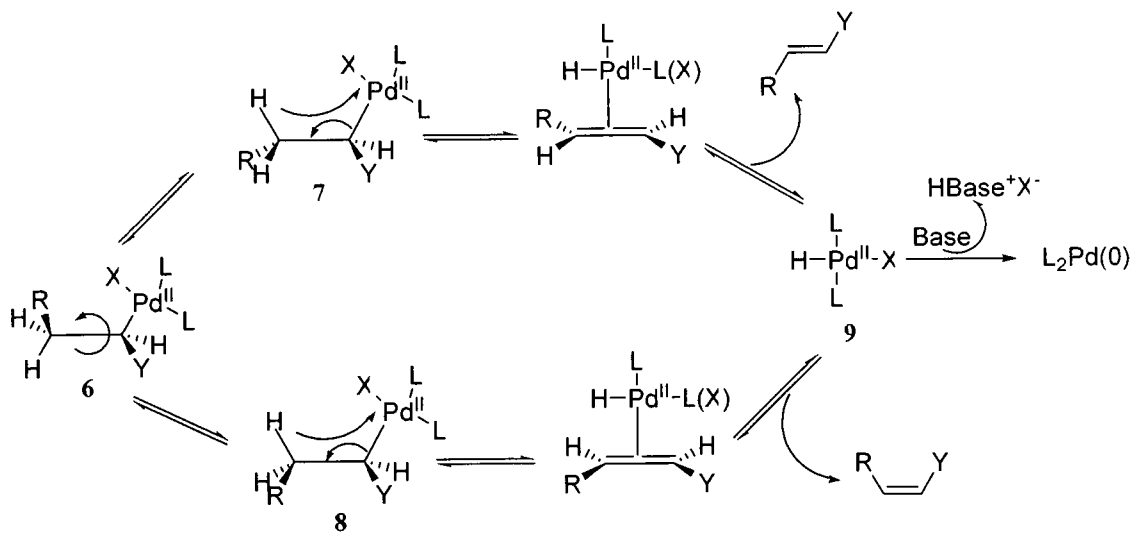
3) in the same manner as 2), RPdX or RPd^+ adds to the double bond, but in this instance the process is a concerted, or S_N2 mechanism. The transition state in this concerted process is electronically adaptable, indicating that it

is in fact steric factors, not electronic ones, that determine selectivity if this possibility were true.

Evidence from data collected on the reactivity and selectivity of the migratory insertion step suggests that the electrophilic behaviour associated with $ArPd^+$ and ArPdX has little or nothing to do with a positive charge. It is assumed that insertion is a concerted process which the reaction path can adapt according to the existent electronic properties, steric factors, or other types of bonding offering some kind of stabilisation (*e.g.* agostic bonds, allylic bonding).[21]

1.6.5. β-Hydride Elimination

The olefin product is then released through β-hydride elimination, where palladium complex **6** (Scheme 1.07) undergoes an internal rotation with the palladium centre in the *syn* position to the β-hydrogen, inducing two possible palladium(II) species, **7** and **8** (Scheme 1.07).



Scheme 1.07. β-hydride elimination can produce a *cis* or *trans* product.

It is believed that it is the *syn*-elimination that defines stereoselectivity of the Heck reaction. Palladium species **7** has an R group *trans* to Y, whereas species **8** has an R group *cis* to the Y.

Elimination obeys the Curtin-Hammett kinetic control principal[169] where the relative energy of the transition states **7** and **8** determine the ratio of *E*- and *Z*-isomers. The species **7** is sterically more stable, hence the *E* olefin is generally favoured. The Pd-hydride complex **9** is still coordinated to the alkene, and must be eliminated fast by the base to release the double bond, *i.e.* the Heck product.

1.6.6. Palladium Regeneration

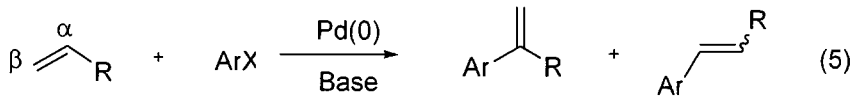
If Pd-hydride is not scavenged fast by the base, it will attach onto the double bond again and it can add onto the end of the double bond yielding a new intermediate; so effectively the PdH can keep passing further along the chain (Scheme 1.08).

Scheme 1.08. Re-additon of PdH down the unsaturated chain.

PdH may even add to the starting alkene, a more attractive option as it is smaller than the Heck product. This process results in the isomerisation of alkenes, which leads to the formation of Heck products with the wrong stereochemistry.[170] An efficient scavenger base eliminates HX *via* [Hbase]X formation, and Pd(0) is regenerated, consequently closing the cycle.

1.7. Heck Arylation of Electron-Rich Olefins

Thus far, most of the reported Heck reactions have employed electron deficient olefins, for example those bearing electron-withdrawing substituents such as $-CO_2R$ and -CN, which selectively yield the terminally arylated or vinylated product at the β-position of the double bond. This position is usually less substituted, and therefore sterically favoured in terms of the arylation or vinylation reaction.[21,122,149,151-153,156,171-177] Although the reaction works well for this class of olefin, there is less documented research into the arylation or vinylation of electron rich olefins (olefins bearing electron-donating substituents). With these electron-rich olefins, for example, acyclic enol ethers, silanes, and enol amides, a mixture of linear and branched regioisomers usually result, thus hampering their wider application in synthesis (Eq. 5).



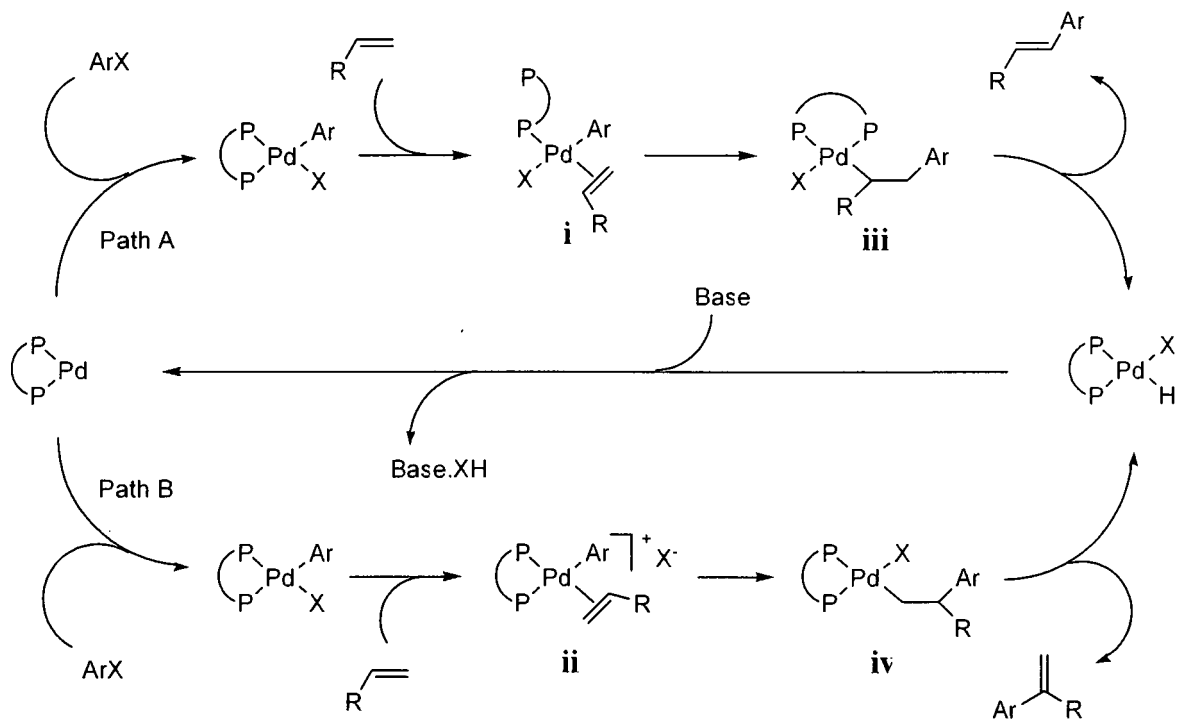
R^1= EWG, EDG

X = I, Br, OTs, OTf

In 1978, Heck and Ziegler[178] reported poor regioselectivity when arylating *N*-vinylpyrrolidone with bromobenzene. Using a monophosphine tris-*o*-tolylphosphine ligand (P(*o*-tol)$_3$), the reaction produced a mixture of regioisomers, *N*-(2-phenylvinyl)pyrrolidone (the β-product) and *N*-(1-phenylviny1)pyrrolidone (the α-product) in a 3:2 ratio. Replacing the ligand with a more bulky tris(2,5-diisopropylphenyl)phosphine ligand yielded the same ratio, suggesting that it was controlled by electronic factors. Another example of poor regioselectivity can be seen with the reaction of 4-bromoanisole and butyl vinyl ether, catalysed by the Herrmann-Beller palladacycle, formed *in situ* from mixtures of Pd(II) salts and P(*o*-tol)$_3$. The α/β

product ratio was 10/13. It was found, however, that addition of an ammonium salt additive improved selectivity slightly.[179] Few catalyst systems exist which allow complete regioselectivity towards the branched product in the arylation of electron-rich olefins with aryl halides ArX (X= I, Br, Cl) without the need for special additives, which includes heterogeneous catalytic systems also.[180]

Poor regioselectivity was experienced by many groups with regards to the Heck arylation of electron rich olefins. It was research by the groups of Cabri, [151,179,181-183] Hallberg[184,185] and others[186-192] who pushed the frontiers of this chemistry further. It was pioneering work by Cabri and coworkers, who demonstrated that selective internal arylation could be affected if certain factors were respected, for example, the choice of leaving group, the use of bidentate phosphine ligands and addition of salt additives. These results lead to the proposition that two routes were in existence in the Heck reaction, a so-called ionic pathway and a neutral pathway (Scheme1.09).



Scheme 1.09. The two pathways of the Heck reaction.

Pathway A follows the same route as the conventional Heck reaction, and Pathway B varies from A with one fundamental difference: the dissociation of the halide or anionic ligand to produce a cationic complex. The olefin occupies each of the coordination sites of the square planar complexes in **i** and **ii**, with the next stage in the process involving R migrating onto the π-system. Therefore, control of the catalyst is dependent on the remaining two ligands; in complex **i**, one neutral phosphine ligand and one anion (X) remains, yielding an overall neutral complex leading to pathway A. On the other hand, if both the remaining ligands are neutral, the cationic complex **ii** is produced in pathway B. In the case of the Heck reaction of olefins by aryl iodides, aryl bromides, aryl chlorides, or the corresponding vinyl halides, in the presence of monodentate phosphines (*e.g.* PPh_3 or $P(o\text{-}Tol)_3$), after oxidative addition onto the Pd(0) square planar complex, a weak Pd-PR_3 is formed as well as a strong Pd-X (X= I, Br, Cl) bond to the slightly electron poor palladium centre. It becomes apparent that for olefin insertion to occur, the dissociation of a neutral ligand (complex **i**) is more likely rather then the halide. There has been much evidence that the use of bidentate ligands slows down the reaction, so in the case of aryl or vinyl halides, where competitive coordination of ligand occurs, no coordination site becomes available for olefin insertion.[182,183,186]

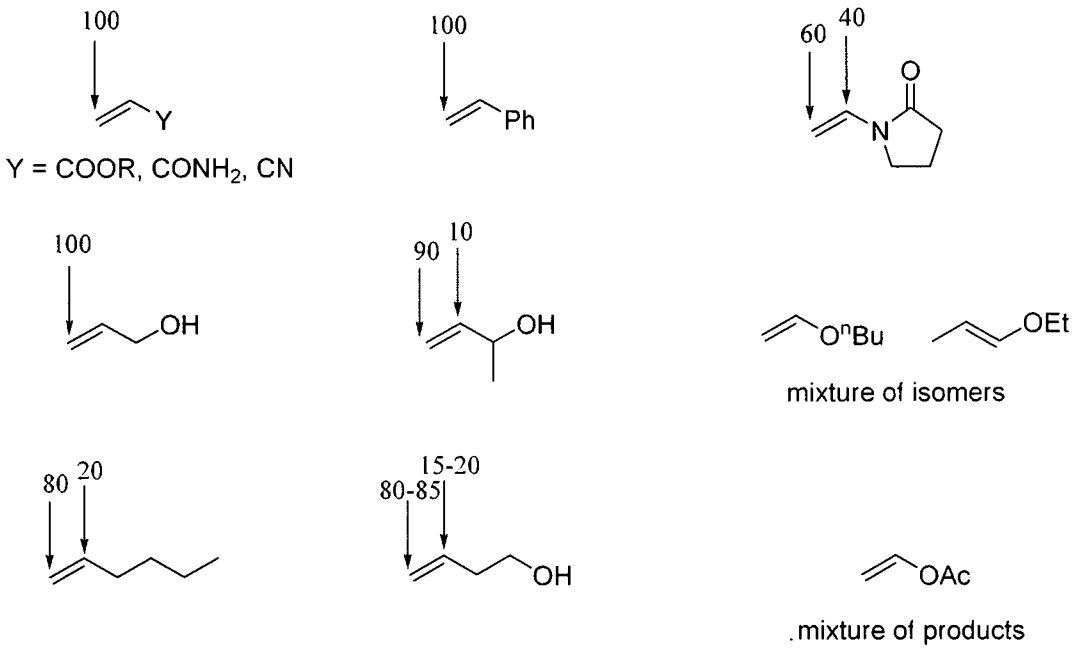
Regioselectivity is related to the coordination/insertion step of both pathways. Steric factors predominate with the migration of the R group in complexes **i** and **ii** to the less substituted carbon resulting in the formation of the linear products. When the reaction proceeds *via* dissociation of the counterion in pathway B, electronic factors predominate because the coordination of the π-system in a cationic complex **ii** induces an increase of the polarisation, and selective migration of the aryl moiety onto the carbon with the lower charge density is observed.[151]

It can be seen why bidentate ligands facilitate α-arylation, and when used in combination with a good leaving group or halide scavenger, excellent regioselectivity towards the branched product is achieved. Hayashi[183,186] and Cabri[151,183] initially proposed that the cationic complex leads to the branched product, and could be induced from the use of triflate as a leaving group.[187,188,191,192] The Pd-X bond is labile when X is a triflate, thus allowing facile dissociation of anionic halide X, forming cationic complex **ii** which leads to the branched product. Electron poor olefins are good π-acceptors, but poor σ-donors, and react faster when the neutral pathway is in operation. The opposite is true for electron rich olefins, in which the cationic species reacts faster with the coordinating olefin as they are good σ-donors, but bad π-acceptors.[182] The π-back donation from the metal to the olefin is higher in a neutral complex **(i)** than in a cationic one **(ii),** resulting in a favoured coordination of the electron-poor olefins. This explains why the use of triflates promotes pathway B; yet there is one more parameter that will lead to the branched product, and this is from the addition of halide scavengers.

The pathways are interchangeable so it is possible to manipulate the reaction conditions, for example, the addition of halide anions to the reaction with aryl triflates, where the labile Pd-OSO_2R is replaced by a strong Pd-X (X=I, Br, Cl), promotes pathway A. It is also possible to induce pathway B by adding stoichiometric amounts of thallium or silver salts, usually in the form of TlY or AgY (Y= nitrate, carbonate, phosphate, acetate, triflate, *etc.*) to the reactions of aryl or vinyl halides.[192,193] The strong Pd-X bond is replaced by a more labile Pd-Y.

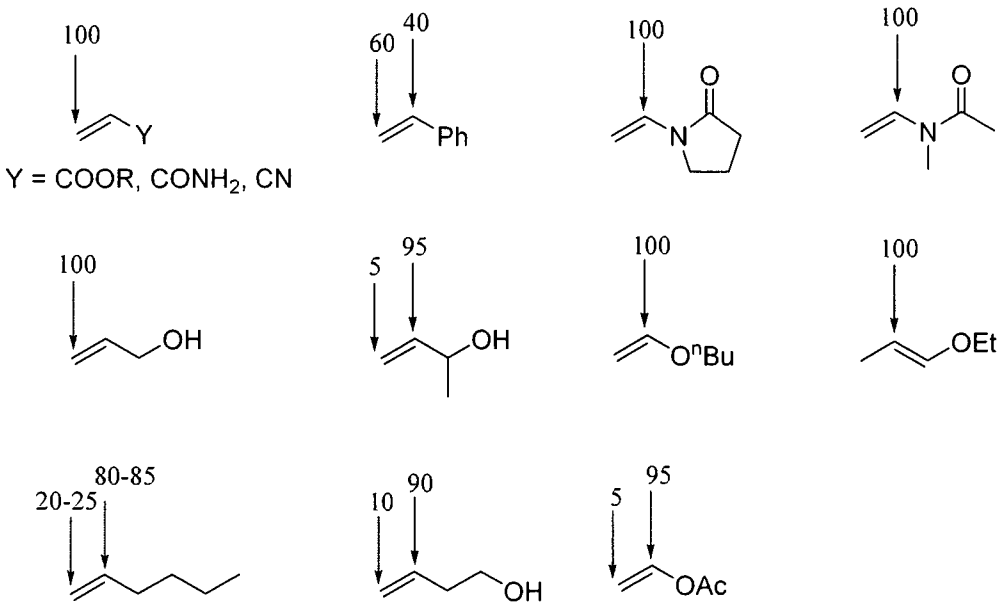
Scheme 1.10 illustrates how regioselectivity can differ in the arylation of different olefins if conditions for Pathway A are followed, *i.e.* the dissociation of a neutral

ligand. Olefins bearing an electron withdrawing group (-COOR, -CN, *etc.*) generate exclusively linear products following pathway A.



Scheme 1.10 Regioselectivity varies for different olefins following Pathway A.

For olefins bearing electron donating groups a mixture is produced when pathway A is followed, the majority of which are linear. Scheme 1.11 depicts the regioselectivity differences when pathway B is followed with the use of bidentante ligands (DPPP, DPPF, *etc.*), triflates or halide scavengers.



Scheme 1.11 Varied regioselectivity for differing olefins when following Pathway B.

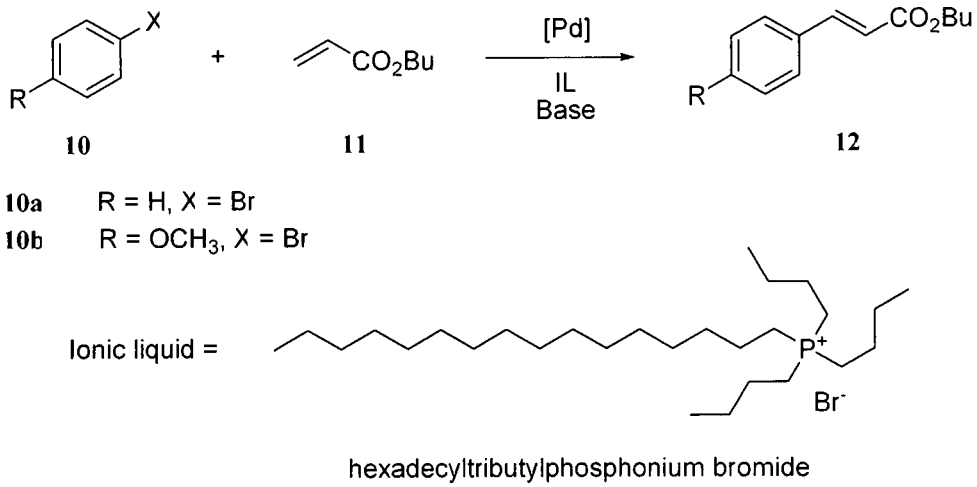
Those olefins bearing electron-donating substituents under the conditions of the ionic pathway show a complete reverse in selectivity, and products are predominantly branched. Functionalities on the aryl ring make no difference to selectivity, nor does temperature or pressure. [192,194-197]

This insight into the Heck mechanism and its parameters allowed research in this field to progress. Even though the regioselectivity issue can be overcome, there are problems associated with the methods; triflates are generally commercially unavailable, base sensitive, and thermally labile. Silver salts add cost to the equation, and thallium salts are toxic. In addition, copious amounts of salt waste are produced which must be correctly disposed of. There is a now powerful incentive to avoid using methods that are not sustainable; so there is a drive to find newer simpler methods that can maintain selectivity, and are accessible in a greener manner.

1.8. Heck Arylation of Electron-Rich Olefins in Ionic Liquids

The Heck reaction can proceed well in many types of solvent media, including ionic liquids.[21] In a programme directed at expanding the scope of metal-catalysed reactions in ionic liquids, the Xiao group discovered that the ionic pathway B could be promoted by using ionic liquids as solvent.[103-108,198-206] This is not surprising, as ionic liquids are composed solely of ions, and hence the electrostatic interactions would favour the generation of the cationic complex (see Scheme 1.09, complex **ii**) and the halide anion, over the neutral Pd-olefin intermediate.

Kaufmann and coworkers were the first to demonstrate Heck coupling reactions in tetralkylammonium bromide based ionic liquids (Scheme 1.12).[207]



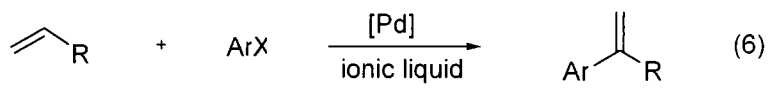
Scheme 1.12. The first example of the Heck reaction in ionic liquids.

They found that the palladium catalysed reaction of bromobenzene (**10a**) with *n*-butyl acrylate (**11**) in the ionic liquid hexadecyltributylphosphonium bromide (or what was then named "melt"), furnished *trans*-cinnamic *n*-butyl ester in high yields, using sodium acetate as an additive which was found to accelerate the reaction, and the base triethylamine (NEt_3). After 24 h, full conversion to **12a** was achieved using

$PdCl_2(PPh_3)_2$, and over 99% yield determined *via* GC. Electron-rich **10b** achieved a yield of 51% of product **12b** in 16 h. In one case where $Pd(OAc)_2$ was the catalyst source in a ligandless reaction between **10a** and **11** in the same ionic liquid, the results of conversion and yield to **12a**, were both > 99% in 43 h.

The observations were also of importance: there was no formation of palladium black, therefore they were able to recycle the catalyst system, with no loss in activity. This suggested that use of phosphonium halide salts as solvent media allows the formation of a long active Pd(0) species, even in a ligand-free reaction.[207]

Results obtained by the Xiao group demonstrated that the unique properties of imidazolium-based ionic liquids could be monopolised as a way of directing reaction pathway. They developed a Pd-catalysed method that allows aryl halides to couple with various electron-rich olefins, furnishing 1,1'-substituted olefins in excellent regioselectivities and yields (Eq. 6).[105-108,198]

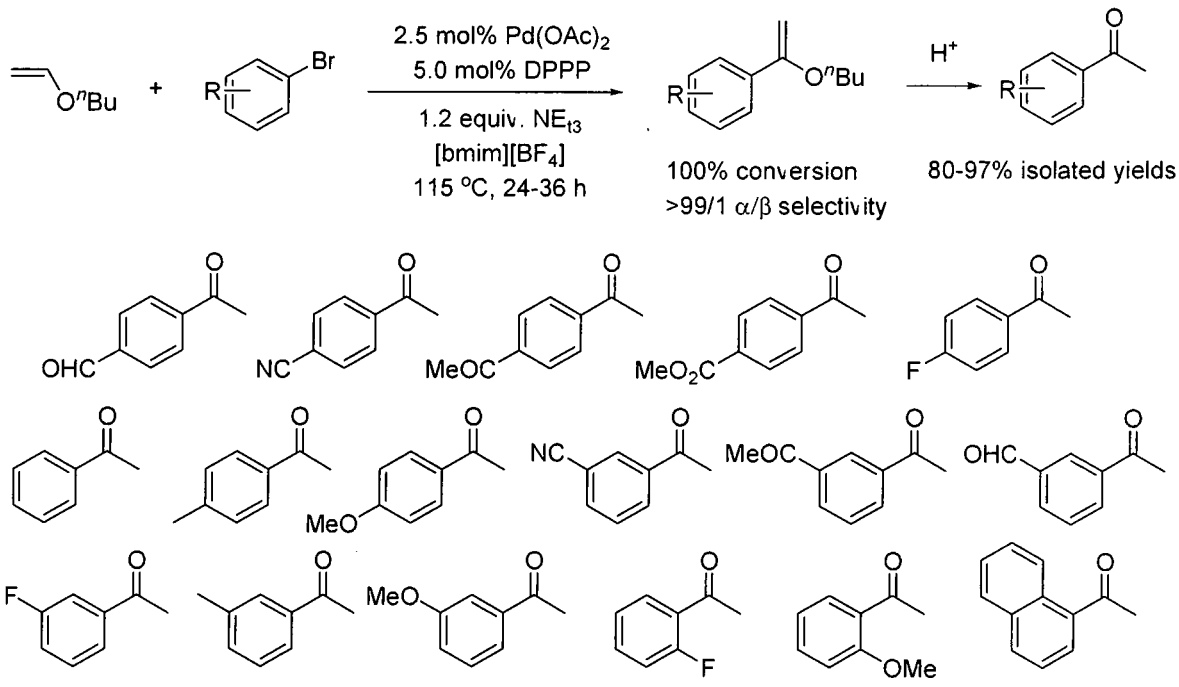


(6)

R = OR', NR'_2, $CH_2SiR'_3$, CH_2OH, CH_2CH_2OH, etc

Until recently, it was thought that under normal conditions vinyl ethers could only achieve regioselective arylation at the internal position by employing aryl triflates or stoichiometric silver or thallium salts.[181,182,193] However, the Xiao group demonstrated that when butyl vinyl ether was reacted with an aryl halide in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) in the presence of NEt_3, $Pd(OAc)_2$ and 2 equivalents of DPPP, a highly regioselective arylation took place, resulting exclusively in the formation of an α-substituted vinyl ether with no need for halide scavengers. Scheme 1.13 illustrates the results obtained. The products were

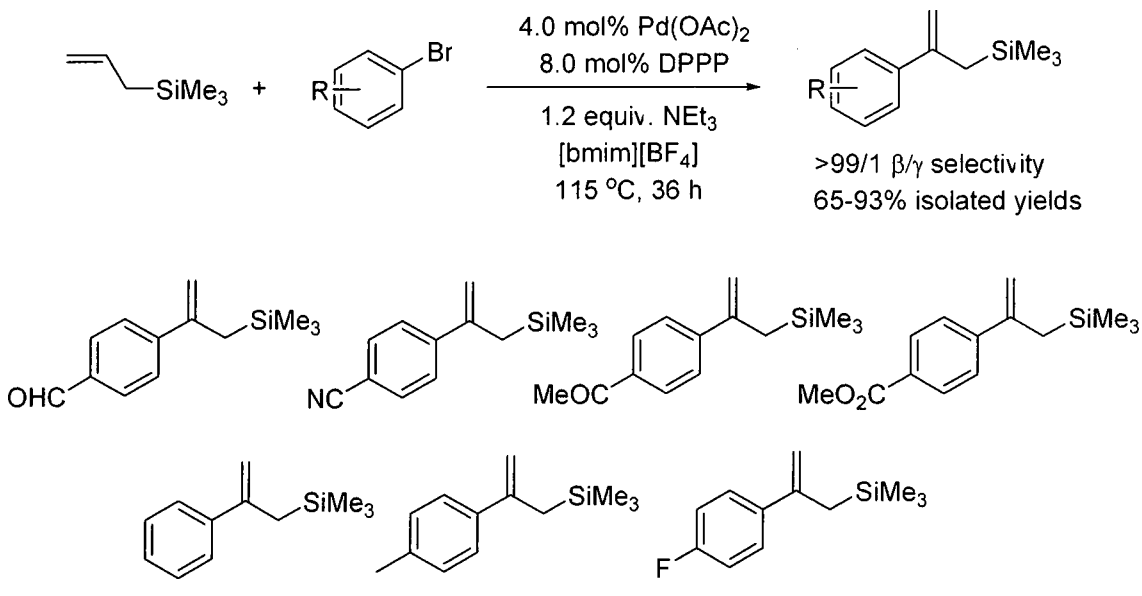
isolated as aryl methyl ketones following hydrolysis of the initially formed branched vinyl ethers. As can be seen, excellent regioselectivities together with high isolated yields for the aryl methyl ketones were obtained in all the reactions in ionic liquid, regardless of the nature of the substituents on the aryl rings. Bromobenzenes bearing either strongly electron-withdrawing or electron-donating *p*-substituents, such as –CN or –OMe, all furnished good to excellent isolated yields with α/β ratios of >99/1. The same reaction can be equally applied to *m*-substituted bromobenzenes having either electron-withdrawing or electron-donating groups. The protocol worked even for some sterically hindered substrates such as the *o*-F and *o*-OMe substituted bromobenzenes, considering that a bulky bidentate ligand is bonded to the palladium centre.



Scheme 1.13. Regioselective Heck arylation of butyl vinyl ether by aryl bromides in [bmim][BF_4] and the resulting methyl ketones.

The remarkable regioselectivities observed in [bmim][BF_4] suggest that the neutral path A (Scheme 1.09) is either completely suppressed or its involvement in the arylation in the ionic liquid is insignificant.

To extend the scope of this highly regioselective Heck chemistry, the arylation of allyltrimethylsilane was also examined (Scheme 1.14). Under traditional Heck reaction conditions, intermolecular arylation of allyltrimethylsilane with aryl halides affords linear arylated silanes, even in the presence of silver additives.[208] In contrast, when performed in the ionic environment provided by [bmim][BF_4], the arylation with aryl bromides of diverse electronic properties proceeded regioselectively to give branched allylsilanes in good to excellent yields. Thus, as shown in Scheme 1.14, the aryl bromides reacted with allyltrimethylsilane furnishing exclusively the β-arylated allylsilanes in 65%–93% isolated yields in the presence of $Pd(OAc)_2$ and DPPP in [bmim][BF_4].



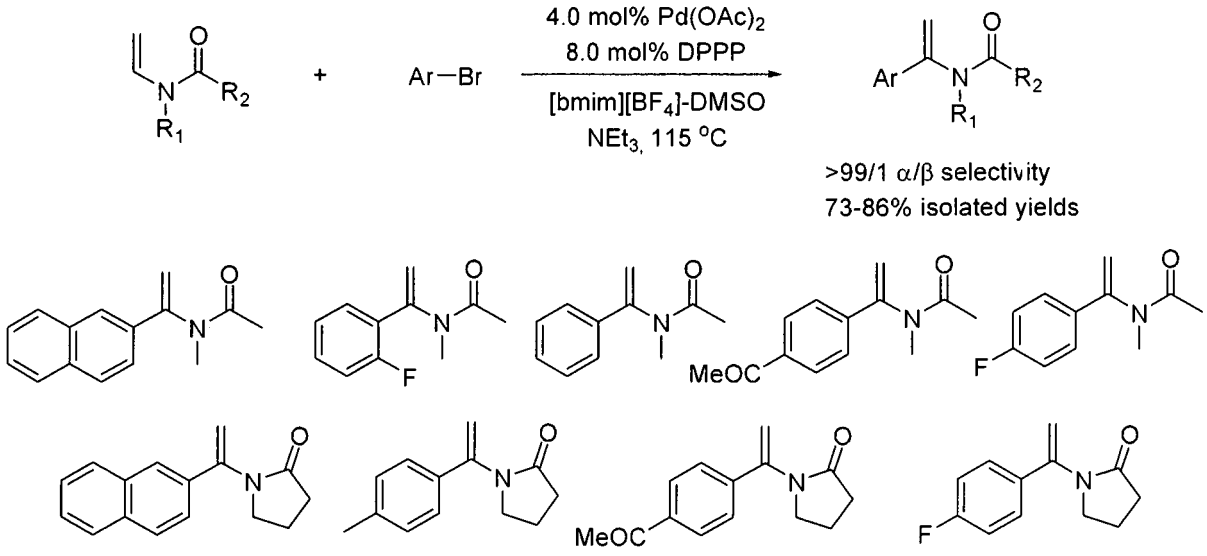
Scheme 1.14. Regioselective Heck arylation of allyltrimethylsilane by aryl bromides in [bmim][BF_4] and the resulting products.

Similar regioselective arylation of allyltrimethylsilane could also be achieved in CH_3CN; but aryl triflates were necessary, according to Hallberg and coworkers.[162] Compared to the protocol in ionic liquid, yields were generally low (31–85%). Hallberg suggested that the reaction proceeds *via* the ionic pathway, the key step being migration of the aryl group to the positively charged β carbon stabilised by the $SiMe_3$ unit, which could be understood as arising from the olefin acting as a nucleophile attacking the electrophilic Pd(II). The excellent selectivities towards the branched products observed in ionic liquid are in line with this view. Any steric effects seem to be completely suppressed or do not exist, as this would yield the less sterically demanding terminally arylated product.

Recently, Larhed and coworkers reported successful regioselective couplings of *N*-methyl-*N*-vinylacetamide with arylboronic acids in 1,4-dioxane, using a phenanthroline ligand with palladium under an atmosphere of oxygen.[209] *N*-methyl-*N*-vinylacetamide showed little sign of coupling with the bromoacetophenone in [bmim][BF_4] when applying the conditions established for the vinyl ether. When DMSO was introduced as a co-solvent, smooth, regioselective arylation took place. Scheme 1.15 illustrates the results obtained with Pd-DPPP in a 1:1 (volume) mixture of [bmim][BF_4] and DMSO.[107]

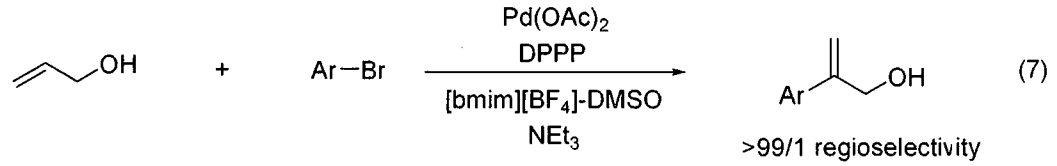
The same reaction in Scheme 1.15 carried out in neat DMSO produced a mixture of different products, in which the branched product was present, but insignificant. In comparison with Larhed's oxidative coupling using the more costly arylboronic acids,[209] the reaction in a solvent-cocktail required harsher conditions but afforded in general higher regioselectivities and higher yields. With both methods, aryl substrates bearing the strongly electron-withdrawing -CN group failed to give good conversions.

The role of DMSO in the solvent cocktail is not entirely clear; it may facilitate β-hydrogen elimination by replacing the coordinated amide from palladium.

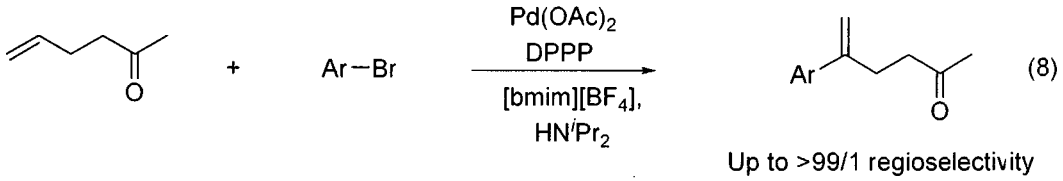


Scheme 1.15. RegioselectiveHeck arylation of enamides by aryl bromides in [bmim][BF_4] and the resulting products.

Recently, our group has also demonstrated that allyl alcohol and 5-hexen-2-one display similar regioselective chemistry with aryl bromides in a solvent cocktail consisting of [bmim][BF_4]-DMSO or in [bmim][BF_4] (Eq. 7 and 8).[104,200] The reaction with allyl alcohol is particularly regioselective, furnishing only the internal arylated allylic alcohols, while that with 5-hexen-2-one provides the δ-arylated δ,γ-unsaturated ketones in regioselectivities of up to 99%.

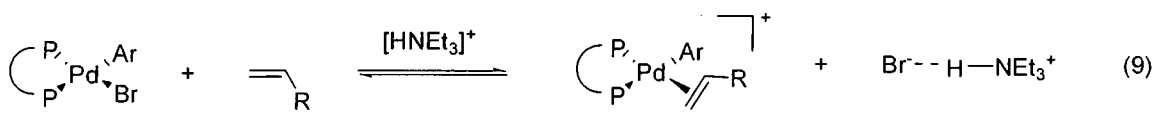


(7)



(8)

The regioselective arylation reactions in ionic liquids can be considerably accelerated by potential hydrogen-bond donating ammonium salts, such as $[HNEt_3][BF_4]$. Further studies by the Xiao group have shown that these salts also enable highly regioselective arylation to take place in common molecular solvents, such as DMF.[200] Their study indicates that the arylation of electron rich olefins by Pd–dppp catalysis is inhibited by bromide ions in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF4]). This behaviour was clearly seen for the arylation of butyl vinyl ether by bromoacetophenone where they observed a dramatic decrease in the arylation rate with increasing bromide concentration, which suggests that there is equilibrium before the rate controlling step (Eq. 9). An important conclusion then is that the HBr generated from each arylation cycle must be effectively scavenged by NEt_3, as the reaction would otherwise be practically stopped before reaching an approximate conversion of 25%. The trapping of the bromide anions could be brought about by possible hydrogen bonding between $[HNEt_3]^+$ and Br^-, thus rendering the equilibrium in favour of the right side (Eq. 9).



(9)

Bromide ions have adverse effect on the reaction of butyl vinyl ether and 4-bromoacetophenone, but introduction of the potential hydrogen-bond donor $[HNEt_3]^+$ was found to enhance the reaction rates. A remarkable illustration of the effect is the comparison between the conversion observed in the presence of 1.5 equivalents of $[NBu_4][Br]$ over 12 hours versus that in the presence of 1.5 equivalents of $[HNEt_3][BF_4]$ over 1 hour; the conversions for the former and the latter were 2 and 78%, respectively! Further evidence in support of the possible involvement of hydrogen bonding came from the observation that replacing $[HNEt_3][BF_4]$ with $[NBu_4][BF_4]$ brought about no significant effect on the reaction rate; but reintroduction of $[HNEt_3][BF_4]$ did considerably accelerate the reaction in $[bmim][BF_4]$.

The effect of such salts presumably arises from the hydrogen bonding capability which helps the dissociation of halide anions from Pd(II), thus promoting the ionic pathway. The unique regiocontrol appears to stem from the ionic environment provided by the ionic liquid solvent or the salt, which alters the reaction mechanism in such a way that the key ionic pathway responsive for the olefin under question is made more favourable.

1.9. Alcoholic Solvents

Synthetic organic chemists are often told that solvent choice is dictated by the chemistry in use, which leads to restrictions in solvent choice. A study was carried out with a data set containing approximately 373 solvents in reactions used to synthesise 38 different complex drug substances, and several conclusions regarding solvent choice were drawn.[36] 50% of solvent usage involves two classes of solvents: alcohols and aromatics. With the addition of polar aprotics, ethers and esters, 78% of

all solvent usage is accounted for. On the basis of the overall data, it might be argued that a choice of 'best-of-class' solvents may be a good starting point for running reactions. A simple example of this might be the case where the literature reaction[36] calls for methanol and xylene, and the 'best-of-class' solvents are determined to be isopropyl alcohol (IPA) and toluene.

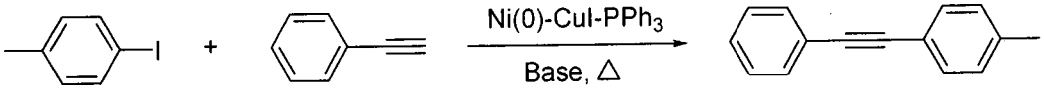
The studies into the hydrogen bond donor-promoted Heck reaction suggest that the ionic pathway may also be made possible by protic solvents, such as alcohols.

1.9.1. Coupling Reactions in Alcohols

With the biodegradability and easy availability, alcohols are also considered to be "green" solvents. However, relatively few coupling reactions have been performed in alcohols as solvent media.

1.9.2. Sonogashira Reactions in Alcohol Solvents

To overcome the incompatibility of lipophilic substrates and inorganic bases, the Sonogashira reaction is often carried out in polar solvents such as DMA and NMP. The use of alcohols as solvents is a cheap alternative to the polar solvents often used. Zhang and coworkers published a paper in 2004, demonstrating the Sonogashira reaction in an alcohol solvent by achieving excellent yields in the coupling of aromatic terminal alkynes and aliphatic terminal alkynes with aromatic, heteroaromatic and vinyl iodides in an isopranol/potassium hydroxide mixture (see Chapter 3.1).[210] The reaction carried out in isopropanol gave a 98% yield, whereas the same reaction in DMSO, 1,4-dioxane and THF yielded 58%, 70% and 23%, respectively (Eq. 10).



(10)

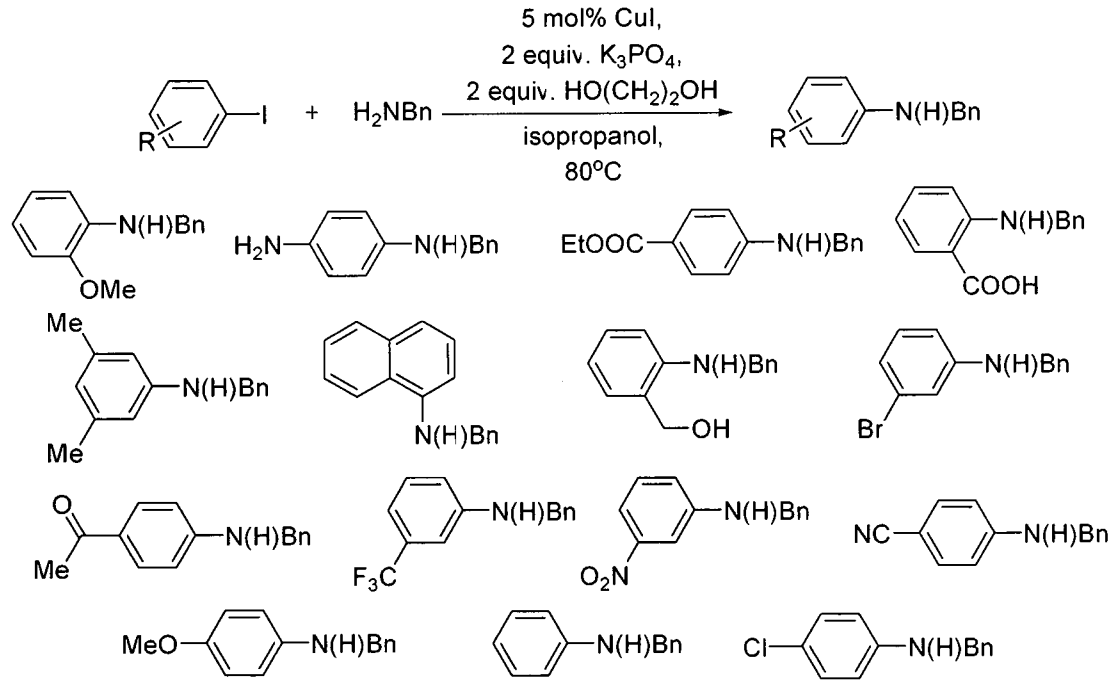
Cai and coworkers conducted a rapid copper- and ligand-free Sonogashira reaction, performed in an oil-in-water microemulsion which is a thermodynamically stable, isotropic, optically transparent solution consisting of water, oil, and a surfactant which can cosolubilise great amounts of hydrophilic and hydrophobic compounds. The ligand-free Sonogashira reaction of iodobenzene with phenylacetylene was also performed in water. A study which examined the influence of alcohols of differing chain lengths was then conducted in which rate and conversion were both found to be far superior then the reactions in water and commonly used solvents. Increasing the chain length improved the reaction rate; for example, replacing ethanol with butan-1-ol increased the yield from 93% to 97%. In this study, the chain length of the alcohol has an important effect on the structure and reactivity of microemulsion systems, where the addition of water-soluble alcohols to water modifies its polarity. In conclusion, it seems that increasing the hydrophobicity of the alcohols leads to a better contact between the reactants at the oil–water interface, thereby resulting in more collisions between them, and therefore enhancing the rate.[211]

1.9.3. C-N and C-S Coupling Reactions

Buchwald and coworkers developed an operationally simple CuI-ethylene glycol catalysed amination reaction taking place in isopropanol, providing a more cost-effective process than the Pd-phosphine system commonly employed. This method takes place under relatively mild reaction conditions and can endure a broad

functional group tolerance on aryl iodides or bromides as coupling partners, taking up to 5-72 h to complete with good to excellent yields. The preliminary experiments showed 2-propanol and *n*-butanol yielded the best reults, while toluene, dioxane, and DMF were much less effective, and ethylene glycol acts as a ligand. This amination protocol can be performed in air, without compromising the yield (Scheme 1.16).[212]

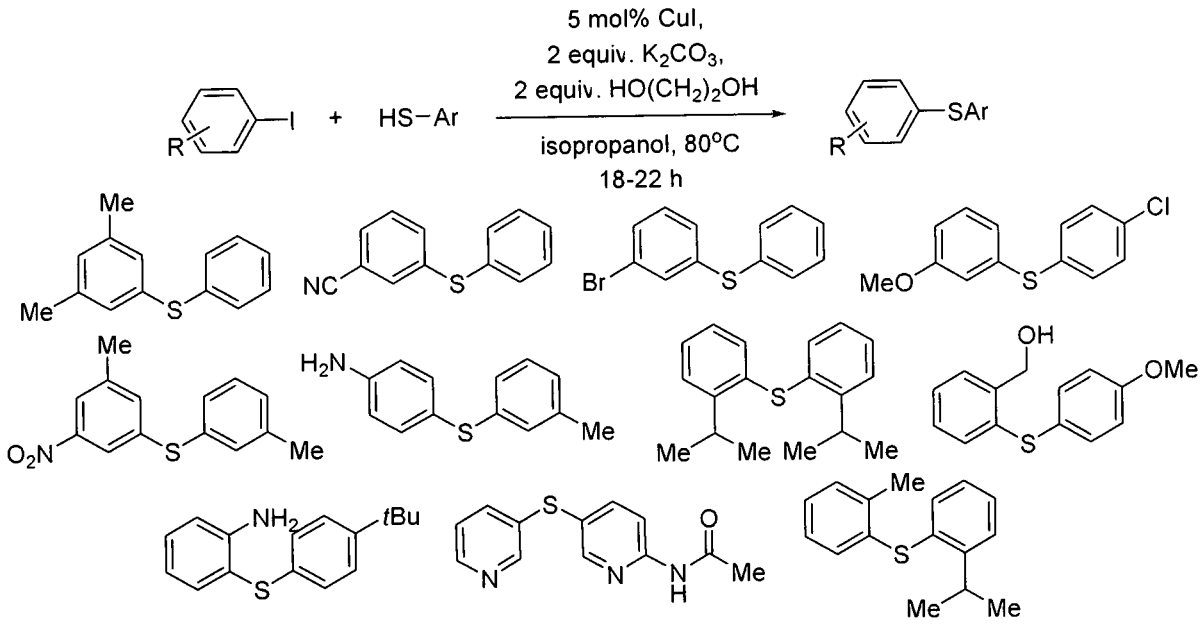
The reactions described in Scheme 1.16 represent those which were carried out in 2-propanol, as *n*-butanol gave slightly slower reactions and lower yields. All reactions in 2-propanol finished in 8-24 h, and yields of 70-91% were obtained.



Scheme 1.16. Products of the copper catalysed amination of functionalised aryl iodides with benzylamine.[212]

Buchwald and coworkers also reported in the same year an efficient copper-catalysed C-S bond formation reaction (Scheme 1.17).[213] Methods for the formation

of aryl sulfides, which are of value to the pharmaceutical industry, have never been popular, especially compared to other palladium mediated cross-coupling reactions. Transition metal-catalysed routes in the construction of aryl-sulphur bonds necessitate harsh reaction conditions, or demanding substrates with *ortho* carbonyl groups that are both electron withdrawing and capable of chelating copper and heterocylic substrates.[214,215]



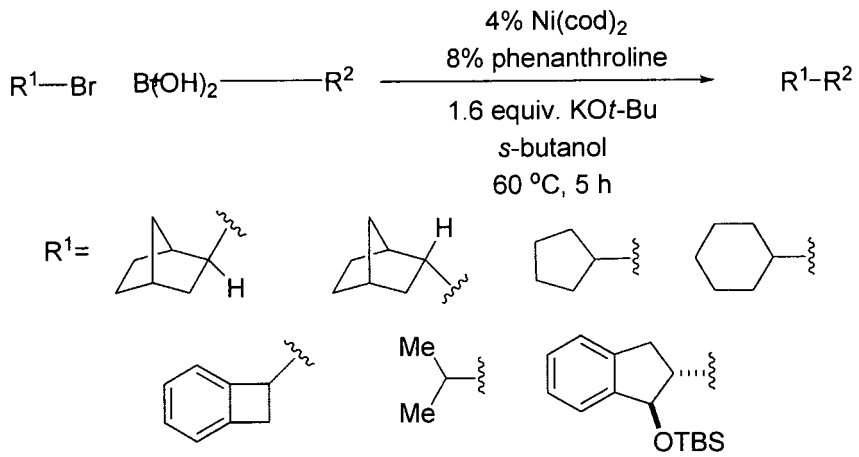
Scheme 1.17. Examples of products from copper catalysed sulphur-carbon bond formation.

Cu(I) rather than Cu(II) was found to be the best source of catalyst, with an added advantage of being stable in air. After optimisation studies, it was found that 2 equivalents of ethylene glycol in isopropanol provided an active and general catalyst system. Presumably, ethylene glycol serves as a cosolvent and ligand in the reaction. Its major function may be to coax and keep the Cu(I) species in solution. Moderate results were obtained using DME, DMF, or dioxane as a solvent in the absence of any

additional ligand. The process is extremely tolerant of functional groups, and high yielding (84-93%). This method is particularly noteworthy given its experimental simplicity, high generality, and the low cost of the catalyst system.

1.9.4. Suzuki Reactions

A recent example of a Suzuki coupling reaction taking place in *s*-butanol is documented by Fu and coworkers. They provide a direct route for the cross-couplings of unactivated secondary alkyl halides with boronic acids (Scheme 1.18).[216]

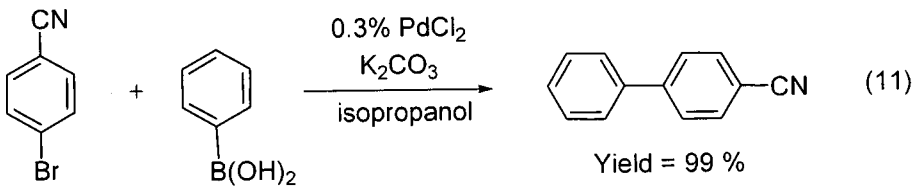


Scheme 1.18. Suzuki cross-coupling of a secondary alkyl bromide.

This procedure allows for electron-rich and electron-poor easy-to-handle arylboronic acids, along with certain heteroarylboronic acids, to be coupled and be applied directly to Suzuki cross couplings, achieving the first Suzuki reactions of unactivated secondary alkyl bromides and iodides. The capacity to employ alkyl electrophiles as coupling partners will markedly increase the already exceptional utility of cross coupling reactions.[216] It is not quite clear what the role of *s*-butanol is

in this reaction; however, it provides another example of the scope of reaction which are possible in an alcohol.

Dong and coworkers have found a highly efficient system to carry out Suzuki cross-coupling reactions of aryl bromides with boronic acids in a ligand-free $PdCl_2$ catalyst system taking place in isopropanol under an argon atmosphere.[217] The use of isopropanol as the solvent makes this system very attractive in view of its low cost and environmental friendliness, but also was found to decrease homocoupling quite dramatically. Yields obtained were excellent, giving 80-99% of the desired product in 4-6 h. A selected example of the cross-coupling of 4-bromobenzonitrile, with phenylboronic acid is illustrated in Eq. 11.[217]



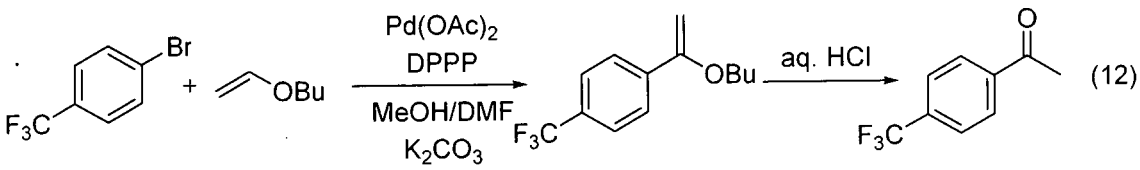
(11)

The role of isopropanol in these reactions is thought to reduce $PdCl_2$ to the active Pd(0) species, where PdX_2 reacts with isopropanol in the presence of base generating a palladium isopropanolate intermediate (see Scheme 1.20).

1.9.5. Heck Reactions

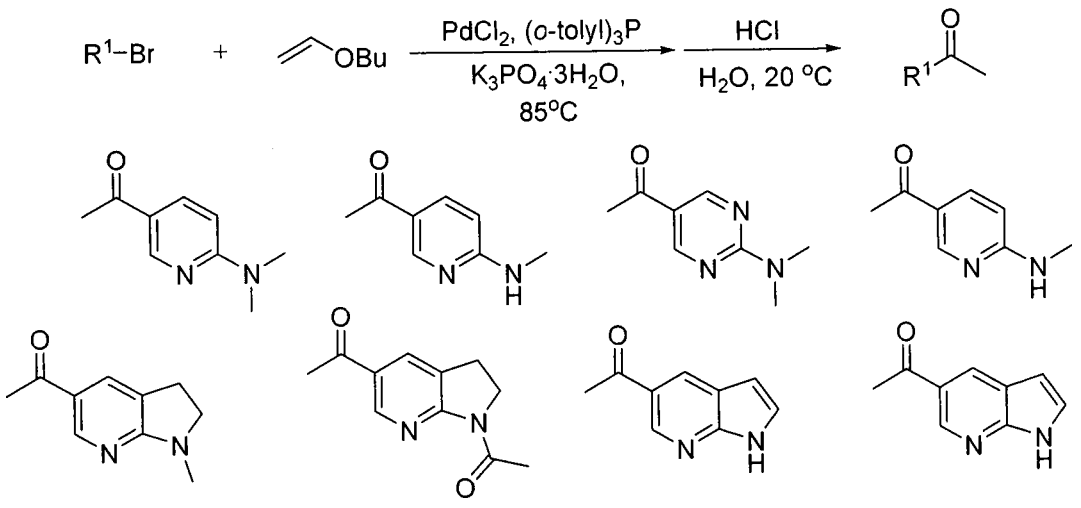
In 2001, shortly after our group reported the use of ionic liquids for the Heck reaction of electron-rich olefins,[205] Hallberg and coworkers developed a procedure which probed the potential of water as a cheap and environmentally friendly polar additive to increase the polarity of a DMF-based reaction mixture. The increase in polarity would support the ionisation and formation of the intermediate cationic complex leading to the branched product when aryl halides are used in conjunction

with electron rich olefins (Scheme 1.09). The efficient conversion of aryl bromides to acetyl arenes was described, remarkably in the absence of thallium and silver additives, provided that the arylations are conducted in an aqueous DMF medium with potassium carbonate as base and DPPP as ligand. One example was included, which replaced water with methanol, in a 3.0/12.5 volume ratio where MeOH acts as the additive, giving a 99/1 α/β selectivity and a moderate yield. This example is given in Eq. 12, illustrating the arylation of butyl-vinyl ether with 1-bromo-4-(trifluoromethyl)benzene.[218]



(12)

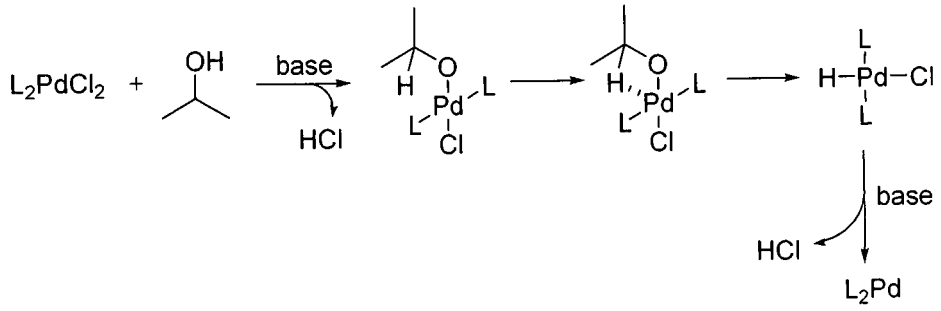
Following these findings and recent work described in Chapter 3, He and coworkers reported a simple and eco-friendly method for the synthesis of functionalised heteroaryl methyl ketones, from a range of heterobromides and butyl vinyl ether.[219] After finding that the coupling yielded none of the desired branched product in acetonitrile, they decided to use a $PdCl_2$/isopropanol catalyst system, much like the system we propose (Chapter 3). Some selected examples of their results are summarised in Scheme 1.19.



Scheme 1.19. Heck arylation of heteroaryl halides with butyl vinyl ether.

The yields varied from 55-75%; but those heteroaryls containing an amine group in the *para* position to the bromide could not be arylated. The authors proposed that the success of $K_3PO_4 \cdot 3H_2O$ as base in the reaction is consistent with the recently documented 'ionic' versus 'neutral' pathways which are believed to be involved in the Heck reaction of electron-rich olefins. One idea that arose from the studies was the added role of isopropanol as a reductant as well as an excellent solvent, which they believed is involved in the reduction of $PdCl_2$ to the active species $Pd(0)L_2$.

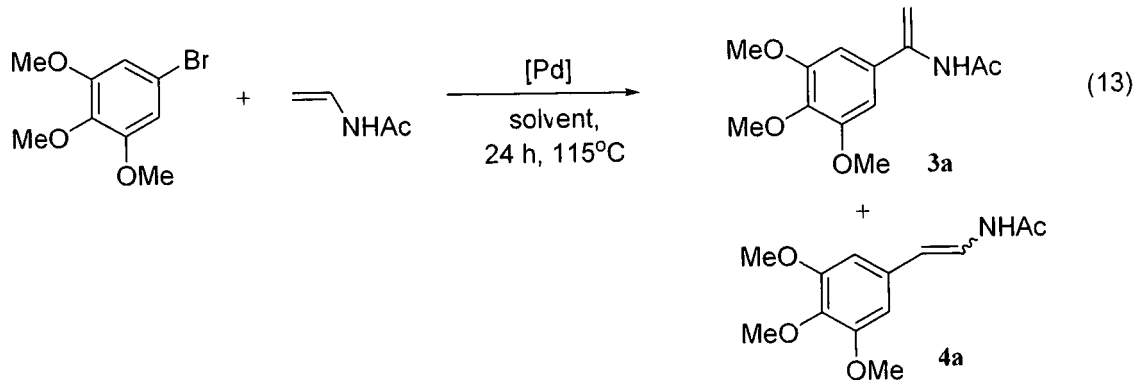
Scheme 1.20 depicts the reduction of L_2PdCl_2, which reacts with isopropanol in the presence of base, in this case, K_2CO_3, where a palladium isopropanolate intermediate is generated. Elimination of the β-H from the intermediate forms a L_2PdHCl species and acetone. HCl is eliminated from L_2PdHCl, thus producing a $L_2Pd(0)$ species, the proposed active catalytic species for the reaction.[219]



Scheme 1.20. Proposed reduction of Pd(II) to the active Pd(0) by isopropanol.

The second paper to be published on the basis of our work, is one by Xu and coworkers,[220] which incorporated the use of isopropanol together with a hydrogen-bond donor salt. In our past studies, the use of an ammonium-based hydrogen bond donor salt was found to promote the ionic pathway, and significantly reduce reaction times, yielding TONs and TOFs that had never been seen for this type of coupling reaction.[200] In this publication, Xu and coworkers reported the regioselective Heck arylation of the electron-rich olefin *N*-acyl-*N*-vinylamine lacking an *N*-alkyl substituent with aryl halides in the presence of the hydrogen-bond donating $[H_2NiPr_2][BF_4]$. The reaction can be carried out smoothly in isopropanol, exclusively generating the branched products in high yields. The arylated enamides are important precursors in the synthesis of optically active amines by transition-metal catalysed asymmetric reactions.[221,222]

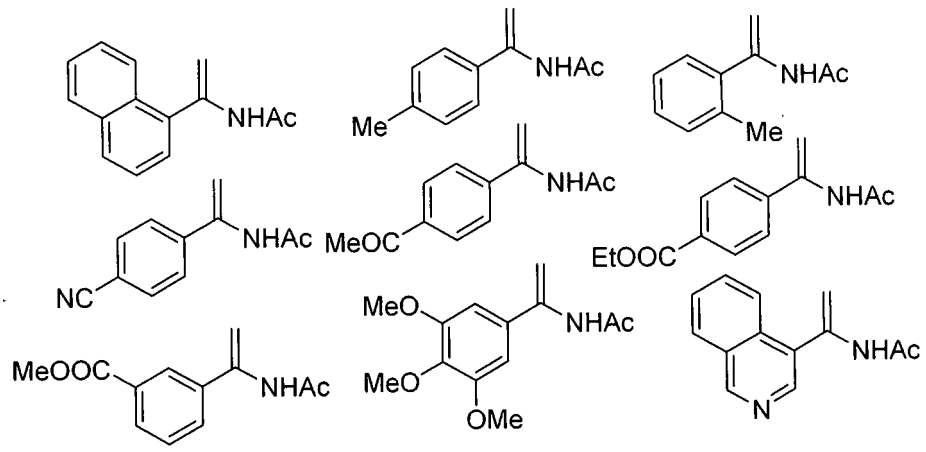
Eq. 13 illustrates the initial solvent screening reaction. A series of seven solvents were tested which are typically used in Heck arylations, including $[bmim][BF_4]$, $[bmim][BF_4]$/DMSO, 1,4-dioxane, DMF, toluene, DMSO and isopropanol, to obtain the desired branched product **3a**. Surprisingly, no reaction was observed in $[bmim][BF_4]$ and $[bmim][BF_4]$/DMSO and the other solvents were very low yielding (17-37%).



(13)

Upon addition of 1.5 equivalents of the salt $[H_2NiPr_2][BF_4]$, full conversion were again reached for those solvents not containing ionic liquid, with yields improving slightly (25-50%). No reaction occurred in the ionic liquid with the salt additive, whereas the ionic liquid/DMSO cocktail faired a little better, affording a 10% yield. Isopropanol showed the greatest promise, increasing from a yield of 37% (no salt additive) to 50% (with 1.5 equiv. additive), and when the additive amount was increased to 10 equivalents, a 92% yield was achieved in isopropanol.

Scheme 1.21 depicts the products formed from the optimised reaction condtions, using 3 mol% $Pd(OAc)_2$, 6 mol% DPPP, NEt_3 as a base, and 10 equivalents of the ammonium salt, in isopropanol. The reaction times varied from 5-19 h for bromides and iodides, with yields ranging from 71-92%, whereas the coupling of aryl chlorides required longer times of 45 h, and low yield were achieved (32-41%).



Scheme 1.21. Products of the Heck arylation of *N*-vinylacetamides with aryl halides in isopropanol.

When $[NBu_4][BF_4]$ was tested in terms of additive effect, there was only a slight increase in yield compared to the reaction without an additive, whereas the reaction in which the hydrogen bond donating ammonium salt was added saw marked improvement in yield and rate. According to Jutand's recent reports,[157,158] the higher reaction rate is probably due to a higher ionic strength, which favours the formation of cationic Pd(II) intermediate in pathway B (Scheme 1.09), and therefore the product **3a** over **4a** (Eq. 13). However, hydrogen bonding between the additive and the bromide anion may also contribute to the formation of the Pd(II) species as $[NBu_4][BF_4]$ was found to be less effective.[200,223]

1.10. Aims of thesis

The latter part of the 20th Century has seen great strides in developing new and active catalysts for the Heck reaction since its discovery by Heck and Mizoroki.[132-138,141,143-145,148,156,173,174,224] These methods, however, do not lead to a regioselective intermolecular arylation of electron-rich olefins when coupled to aryl halides. The

past two decades has witnessed a new type of arylation reaction, taking place at the internal α-position of the olefinic bond, with the aid of certain factors: triflates, instead of halides, or the use of silver or thallium salts which can act as scavengers when aryl halides are employed (X = I, Br). The proposal for a new mechanism arose, shedding light into why these few factors need to be respected in order to obtain a degree of regiocontrol.[151,181,193] Following this, in recent years, new methods have emerged which make the use of solvent, ionic liquids, solvent cocktails, and other novel reaction media, to promote the ionic pathway in order to afford solely the branched product.[107,192,218] And very recently, our group reported the use of hydrogen-bond donating salts,[200] which can be used in molecular solvents, leading selectively to the branched products and increasing the rate of reaction.

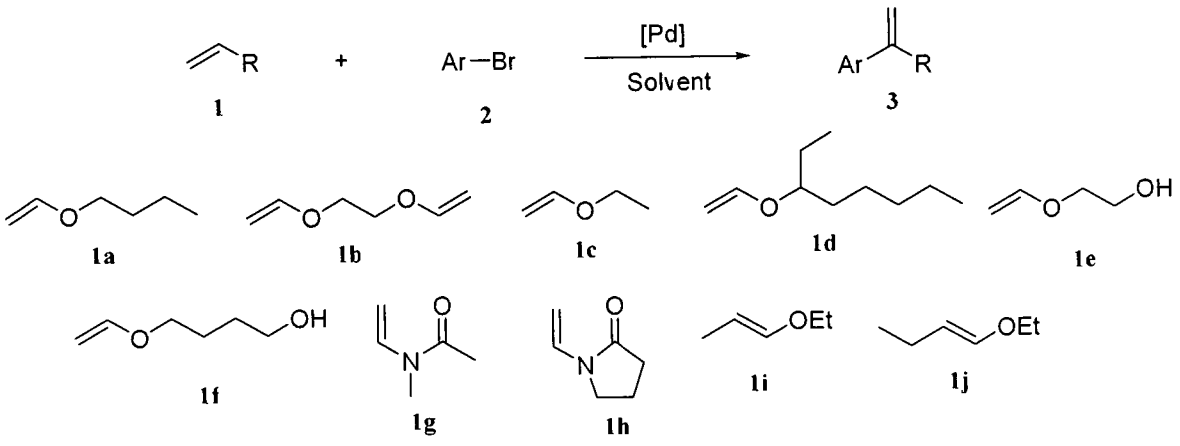
The system developed by the Xiao group allowed the frontiers of this chemistry to be pushed further, and led to the basis of the second chapter. However, ionic liquids are still in their infancy, little is still known about their toxicity[225-229] (Scheme 1.09). Potential hydrogen-bond donor salts accelerated the reaction to a fraction of the time recorded in ionic liquids alone producing turnover numbers (TONs) and turnover frequencies (TOFs) which had not been seen before for this type of arylation. The reaction, however, requires the addition of copious amounts of salts which are not commercially available, and requires the disposal of salt waste.

The other breakthrough of the recent years is the development of catalytic systems employing very low concentrations of catalysts, thus being characterised by huge turnover numbers exceeding millions or even close to billions (also, see Chapter 5). Often very simple catalyst precursors can be used, with additional activation being achieved by advanced techniques, such as microwave heating, allowing for dramatic reductions of the reaction times from days to hours, or hours to minutes. One of the

most serious drawbacks of homogeneous catalysis are the low stabilities of catalysts under reaction conditions, their high cost, and the sophisticated procedures required for post-reaction separation of catalyst from products. These problems can be effectively eliminated by the application of new catalytic systems combining the characteristics of homogeneous and heterogeneous catalysts, such as various biphasic systems, supported catalysts, encapsulated and others, as discussed previously (see section 1.4). Lower catalyst loadings make a reaction more practical, though the vast majority of Heck reactions employ a catalyst loading of >2%, which is too high for economic "green" operations. The question arises: Is it possible to achieve a simple, effective, selective, cheap system, with sustainability towards a greener future?

In an aim to better that which has already been reported, this thesis aspires to achieve a new catalytic system, which allows regiocontrol in the arylation of electron-rich olefins, for which high yields can be obtained, and offers diversity of both olefins and aryl halides. It is also hoped that the catalyst system can allow the reaction to be performed at lower catalyst loadings, with no recourse to halide scavengers, or triflates.

In the course of this thesis we will discover an excellent catalyst system which will allow the successful regioselective arylation of electron-rich olefins in novel reaction media (Scheme 1.22).



Scheme 1.22. The regioselective Heck arylationof electron-rich olefins **1a-j** in novel reaction media.*

* Chapters 2-6 will have the numbering system of Scheme 1.22.

CHAPTER TWO

Direct Regioselective Synthesis of Cyclic Ketals from Hydroxyl Alkyl Vinyl Ethers and Aryl bromides in Ionic Liquids

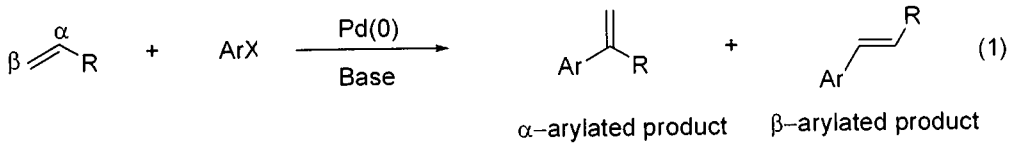
2.1. Introduction

The Heck reaction, which is the arylation or vinylation of olefins by aryl or vinyl halides, comprises one of the most important carbon-carbon bond forming reactions in organic synthesis. The reaction is homogeneously catalysed principally by palladium complexes in solution. [21,122,171,175,177,230] Much of the early research into the coupling of sp^2-hybridised carbons for such syntheses has relied heavily upon organotransition metal chemistry, usually involving low-valent palladium or nickel coupling to a vinylic halide or triflate. This methodology requires further reaction with a preformed alkenyl metal complex, which can be derivatives of zinc, tin, boron, zirconium, silicon, aluminium and magnesium but applies only when the Heck reaction cannot provide regio- and stereocontrol for such cross-coupling reactions in a direct vinylic substitution (see Scheme 1.02).[141,184,185] The popularity of the Heck reaction is attributable to the broad availability of aryl iodides, bromides and chlorides, and the versatility towards a wide variety of functional groups. The reaction has therefore been widely exploited for commercial needs, from fine chemicals to pharmaceuticals.[231,232]

As mentioned previously, the reactions of aryl halides as substrates and in some cases, vinyl halides, have been studied extensively, but most commonly employed coupling partners are electron-deficient olefins, that is, olefins bearing electron-

withdrawing substituents (such as -CO_2R, -CN, and -Ph). Electron rich olefins on the other hand have seldom been exploited, limiting the wider applicability of these reactions in synthetic chemistry.

The family of electron rich olefins comprises acyclic enol ethers, silanes, and enol amides, the reactions with which, when coupling to an aryl halide or vinyl halide, often suffer from poor α/β-regioselectivity which produces a mixture of linear and branched regioisomers (Eq. 1).



Whilst the use of electron rich olefins in Heck arylation reactions is limited, progress made in this area thus far has enabled very regioselective arylation to be performed. Early research by Hallberg[184,185] and Larhed[192,194] and coworkers revealed that the regioselectivity of the palladium-catalysed arylation of enol ethers is sensitive to structure of the enol ether, the arylating agent used, and reaction medium. Control of these factors allows control of regioselectivity for arylation at the olefinic α- or β-carbons of the enol ether double bond. It was also established that electron-rich aryl systems favour α-arylation whereas electron-poor aryls favour β-arylation.

A significant advance was made by Cabri,[151] who recorded α/β regioselectivities of >99/1 with acyclic enol ethers such as butyl vinyl ether in DMF; the key finding here was the use of bidentate ligands, in conjunction with the addition of stoichiometric amounts of silver and thallium salts [Ag(OTf) or Tl(OAc)] which are thought to act as halide scavengers.[21,151,152,172,175,233] Another discovery made by Cabri to attain regioselectivity was the replacement of the dissociating halide with triflates. The chemistry has since been applied to a number of synthetic efforts. The results

obtained by Cabri and others can be rationalised in a simplified mechanism.[21,152,175,181-183,186,230,234-239] This mechanism is now widely believed and accepted, which illustrates that there are two pathways in existence, an ionic and neutral pathway which respectively lead to the branched and linear product if the corresponding factors are adhered to (see Scheme 1.09).

The proposed scheme offers an explanation as to why managing certain factors allow regiocontrol over the arylation at the olefinic α- or β-carbons of the olefinic bond, for example, the use of a bidentate ligand, and stoichiometric amounts of silver and thallium salts or the use of triflates. The principal features which set the two pathways aside is the ligand separation; pathway A portrays the dissociation of one neutral ligand, while pathway B is characterised by the dissociation of halide anions generating a cationic Pd(II)-olefin complex, which is believed to be the key species that gives rise to the α regioselectivity.[151,240-243] Later reported methods suggested the preparation of desired alkoxy dienes through direct palladium-catalysed vinylation of simple vinyl ethers with enol triflates.[161,244,245] Triflates or halide scavengers are expected to assist in the formation of the cationic palladium species and hence the α–arylated products. This is because the rupturing of C-X bond in the oxidative addition step, which many believe is the rate limiting step of the cycle (particularly when X = Cl), is facilitated by the lability of the Ar-OTf, whereas halide scavengers simply "scavenge" the halide from the complex, forcing the all important cationic complex to form. A drawback to the chemistry is that triflates are base sensitive, thermally labile, and are rarely commercially available, and the inorganic silver and thallium salt additive are costly and toxic, respectively. There is also an ever pressing need to abstain from the disposal of copious amounts of salt waste, which could also be toxic. Hence, an alternative method for the arylation of aryl halides with electron-

rich olefins, which circumvents the need for the halide scavengers, while maintaining regioselectivity, would be highly sought after.

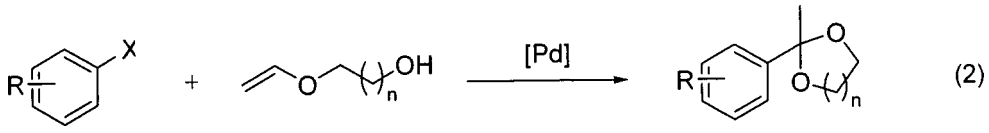
As triflates or halide scavengers are expected to facilitate the formation of the cationic palladium species, we thought that the formation of such ionic species might also be promoted by ionic liquid as solvent because the cationic intermediate would be favoured by electrostatic interactions.[107] In a programme directed at developing metal-catalysed reactions in ionic liquids, our group found that several classes of electron-rich olefins can indeed be arylated highly regioselectively in imidazolium ionic liquids by directly using aryl halides with no need for a halide scavenger.[105-108,201-205] Similar results have also been reported by other groups by using ionic liquid solvents.[100,246]

In this chapter, we report that the Heck arylation of hydroxyalkyl vinyl ethers 2-hydroxyethyl vinyl ether and 1,4-butanediol vinyl ether by aryl bromides can be carried out in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), leading to interesting 5- and 7-membered cyclic ketal compounds in a highly selective manner. Previous methods of synthesis for similar compounds are also discussed. These ketals can be useful as intermediates in the synthesis of anti-HIV agents or as protected precursors for carbonyls, offering stability against nucleophiles and bases.[247,248]

Hallberg and Larhed and coworkers were the first to report the highly regioselective arylation of hydroxy vinyl ethers with aryl bromides, iodides and triflates, to synthesise the cyclic ketals of acetophenones, in DMF.[192] The reactions with aryl triflates and the hydroxyalkyl vinyl ethers 2-hydroxyethyl vinyl ether and 4-hydroxybutyl vinyl ether proceeded smoothly at a mild temperature of 80 °C, affording 5- and 7-membered cyclic ketals. The nine-membered cyclic ketal could not

be isolated from the arylation of 6-hydroxyhexyl vinyl ether, since decomposition occurred during attempted purification on silica.

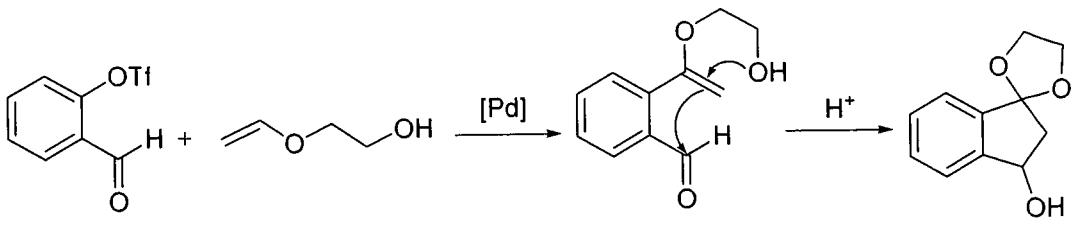
When the reaction involves bromobenzene or iodobenzene, the addition of thallium(I) acetate was required in order to gain regiocontrol. However, the ketalisation process, required 144 h to complete. In the case of iodobenzene, when the temperature was increased to 130 °C from 80 °C after 24 h, the 5-memebered ketal was formed and gave a modest yield of 62%. In those case where the aryl triflate contained an electron withdrawing functionality (-COOH, -CN, -CHO), reactions required the further addition of dry acetic acid to promote ring closing. In no circumstances was the linear product seen (Eq. 2).[192] The experimental procedure is simple, whilst past methods of preparation of 1,3-dioxolanes have required the use of a strong acid catalyst (see also Section 4.2, Chapter 4). However, as already stated, the problem associated with this chemistry is the use of Ag^+, which is expensive, and Tl^+, which is toxic.



(2)

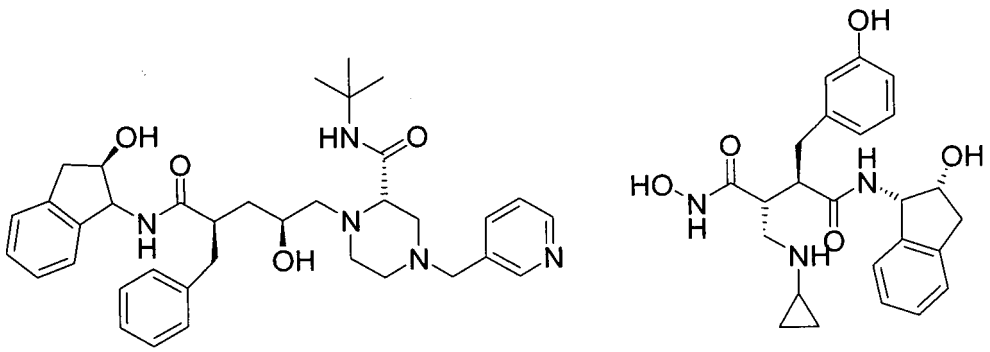
X = OTf, I, Br; n = 1, 3, 4

When the triflate is a derivative of salicyclic aldehyde it can be conveniently converted to 1,1-(ethylenedioxy)-3-hydroxyindans. This is achieved by internal Heck arylation of 2-hydroxyethyl vinyl ether, through subsequent ring closure after the coupling, in a one-pot fashion (Scheme 2.01).[249] This a useful route to the synthesis of indans (Scheme 2.02).



Scheme 2.01. Arylating agents containing an *o*-aldehyde group can produce monoprotected 3-hydroyindan-1-ones.

Indan structures are important components in many bioactive compounds. Two examples of protease inhibitors are illustrated in Scheme 2.02, depicting an aspartyl protease inhibitor indivir, which is an anti-HIV agent, and a matrix metalloprotease (MMP) inhibitor.

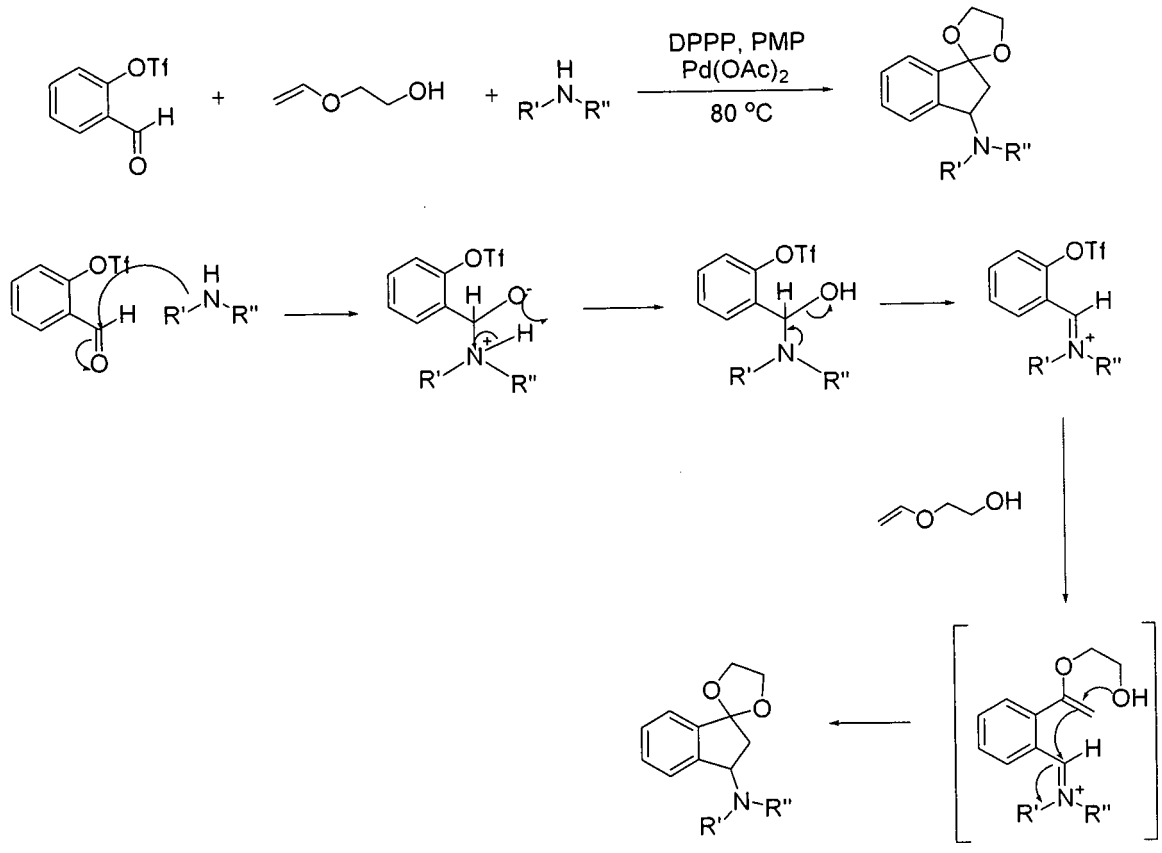


Scheme 2.02. Indinavir and MMP-inhibitor.

Easy access to indans is important, as they are suitable starting structures for further modification.[247,248] The reaction depicted in Scheme 2.01 requires a simple Pd/DPPP system, using PMP or NEt_3 as a base, in DMF, at 120 °C. Once all the starting substrate has been consumed, ring closing is completed upon addition of dry acetic acid at 80 °C.

Hallberg also reported another one-pot three-component reaction, which is very similar in mechanism to Scheme 2.01, involving a set of salicyclic aldehyde triflates,

2-hydroxyethyl vinyl ether, and various secondary nucleophillic amines.[250] Providing useful starting substrates as protease inhibitors, a method for the chemoselective generation of substituted 3-aminoindan-1-ones and the corresponding glycol acetals was achieved (Scheme 2.03).



Scheme 2.03. Proposed pathway for the formation of protected 3-aminoindan-1-one derivatives.

The concentration of amine had to be kept lower than the aryl triflate. Two reasons for this are that the nucleophilic amine coordinates to Pd(II), consequently interrupting the catalytic cycle making the Heck reaction less effective at higher concentrations, and if the concentration is too high, ring closure is inhibited.

This method demonstrates a novel one-pot method for the preparation of protected 3-aminoindan-1-one derivatives from salicyclic aldehyde triflate, 2-hydroxyethy vinyl ether and nucleophillic amines, which relies on the regioselective Heck arylation and subsequent intramolecular nucleophillic attack by the hydroxy ether.[250]

In an instance where the arylation of 2-hydroxyethyl vinyl ether by aryl bromides is carried out in DMF without a halide scavenger, but with an effective ligand, it is possible to obtain the β arylated products. Santelli and coworkers demonstrated this by using a tetradentate phosphine ligand *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphanylmethyl)cyclo-pentane (Tedicyp). In this system it is thought that the enol is anchored to the metal atom by the alcohol functionality which probably imposes a conformation change in the structure of the active catalytic complex. The Pd(aryl)(enol) intermediate is stabilised as a neutral Pd complex. The cationic pathway does not exist, or is completely suppressed, yielding predominantly the linear product. The highest conversions were achieved with sterically hindered aryl bromides, but it is thought that a combination of steric factors as well as electronic factors may have an effect on reaction rates.[251]

There is a growing need to replace toxic, damaging or volatile organic solvents with cleaner, economical and ecological media, the reasons being the sheer volume of solvents used by the chemical industry that can pose serious health and environmental risks, and to rid of volatile chemicals which are difficult to store and dispose of. Ionic liquids have provided a potential solution to the problems. Even though ionic liquids have been present since the early 20th century, only recently has literature offered a significant overview on the properties and aspects associated with their use as novel reaction media, in replacement of organic solvents.[33,39,76,111,252-254]

In particular, room temperature ionic liquids such as those based on imidazolium salts have been recognised as one of the most promising alternatives to hazardous organic solvents for more sustainable "greener" chemical processes, owing to their extremely low vapour pressure and their novel, tuneable physicochemical properties (Chapter 1).[65,83,97,255-262] A great number of catalytic reactions have proved feasible in these ionic liquids,[263-281] with many displaying enhanced reactivities and selectivities, some of which have not been seen in common organic solvents.

Aimed at developing palladium catalysed reactions in ionic liquid, we thought that the formation of the cationic species in Path B (Scheme 2.01) which is imperative in order to obtain the branched product, may also be promoted by ionic liquid. The reasoning behind the hypothesis was the cationic complex would be favoured by electrostatic interactions, over the neutral Pd-olefin intermediate from the same.[108,198,201,202,282]

The ionic liquid [bmim][BF_4], an ambient-temperature, air and water-stable ionic liquid, can dissolve many classical organometallic catalyst precursors such as rhodium, ruthenium, nickel, cobalt, iron, and palladium compounds. Importantly, transition-metal catalyst precursors are not removed by nonpolar organic solvents and remain stable in ionic liquids.[65,76,83,97] Our study started with this ionic liquid.

2.2. Results and Discussion

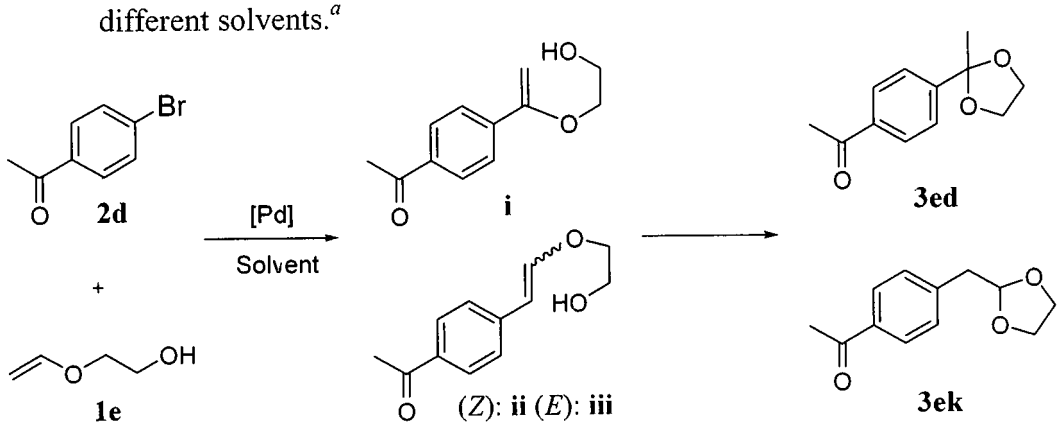
Following the successful arylation by aryl halides of vinyl ethers and other electron-rich olefins in the ionic liquid [bmim][BF_4],[107] we were delighted to find that the hydroxy vinyl ether **1e** could also be arylated in a highly regioselective manner, where the resulting coupled product cyclises to yield cyclic ketals. To the best of our knowledge, this is the first time when hydroxy vinyl ether has been selectively

arylated at the internal α-position by an aryl bromide, without recourse to a halide scavenger (when aryl halides are employed) or the use of triflates.

Initially, we tested the achievability of the reaction in ionic liquid [bmim][BF_4], using aryl bromide 2'-bromoacetophenone, **2d,** and 2-hydroxyethyl vinyl ether, **1e**. A typical reaction consisted of a catalytic amount of catalyst, 3.0 mol% $Pd(OAc)_2$, and ligand, 6.0 mol% DPPP, 1.5 equivalents of base triethylamine, 1.0 equivalent of substrate aryl bromide, and 2.0 equivalents of the electron rich ether. The mixture was heated to 115 °C under a N_2 atmosphere. This reaction was monitored, and was found to reach completion after 22 h, furnishing the 5-membered ketal without subsequent addition of acid (Entry 1, Table 1).

After obtaining this result, a solvent study was carried out in DMF, DMSO, 1,4-dioxane, THF, acetonitrile and toluene, solvents of which are typically used in Heck reactions. The results demonstrate the lack of regioselectivity in the arylation of **2d** with **1e** in molecular solvents, even though high conversions were afforded for entries 1 and 2 (Table 1), but the yields for the α-arylated product **3ed** were low. In sharp contrast to the results obtained in [bmim][BF_4], none of the reactions afforded a similar α/β ratio. DMSO (Entry 2) produced the highest α-regioselectivity consistent with its high polarity which is thought to promote the ionic route.[102,105,283] In the case of dioxane, THF, acetonitrile and toluene the reactions were markedly slower giving rise to a mixture of β- and α-arlyated products (Entries 3-6), and predominantly the more stable *E* isomer when the β-product was detected. These results confirm early observations, that is, mixtures of regioisomers result when electron-rich olefins are arylated with aryl halides in molecular solvents.[148,193,284 151,192]

Table 1. Heck arylation of 4'-bromoacetophenone with hydoxy ethyl vinyl ether **1e** in different solvents.[a]



Entry	Solvent	Conversion[b] (%)	Ratio of isomers[c] **i/ii/iii/3ed/3ek**[d]
1	DMF	99	0/0/0/52/48
2	DMSO	100	0/0/0/89/11
3	1,4-Dioxane	29	2/4/6/34/54
4	THF	20	10/3/5/35/47
5	Acetonitrile	36	2/10/22/45/21
6	Toluene	23	6/24/19/28/23
7	[bmim][BF_4]	100	0/0/0/99/1

Reaction conditions: [a]1.0 mmol **1e**, 2.0 mmol **2d**, 3.0 mol% $Pd(OAc)_2$, 6.0 mol% DPPP and 1.5 equiv. Et_3N at 115°C for 22 h using 2 ml of solvent, analysis was determined ^{1}H NMR from the crude product. [b]Conversion of 2d to **3ed** and **3ek**; [c]α/β ratio of >99/1 was assigned when **3ek** was not detected by ^{1}H NMR. [d]Ratio of *trans/cis* isomers.

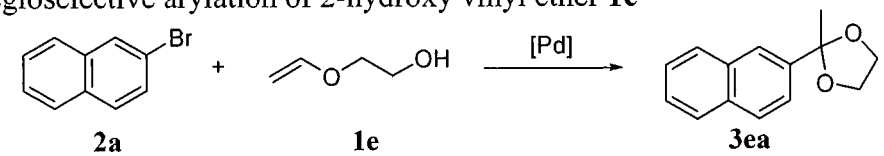
Ionic liquid [bmim][BF_4] was shown to work extremely selectively leading to predominantly α-arylated product ketal **3ed**. In line with our previous reports on the Heck arylation of electron-rich olefins in ionic liquids,[103,105,106] these initial results clearly indicated that [bmim][BF_4] promoted the ionic pathway in the arylation of electron-rich olefin **1e** to give preferentially the α-arylated product. Even if polar solvents such as DMF and DMSO aid halide dissociation from the palladium, and the resulting high concentration of Pd-olefin cations have been shown to give fast rates of

olefin insertion into Pd-Ar bonds,[285-287] it is clear that none of the molecular solvents alone are able to completely alter the reaction pathway. Noteworthy is that palladium black was rarely present at the end of the reaction, whereas in molecular solvents it was quite prominent. Therefore, we can assume that [bmim][BF_4] not only promotes the ionic pathway, but also stabilises the active Pd-phosphine species within the reaction. This promted us into investigating whether ionic liquids could be recycled.

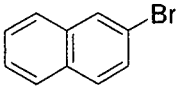
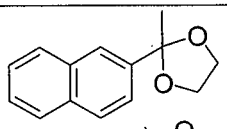
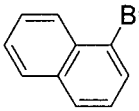
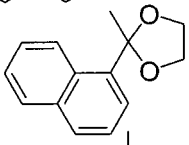
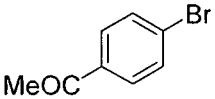
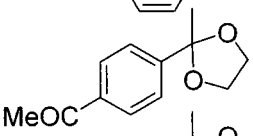
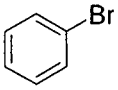
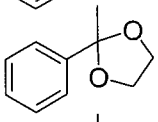
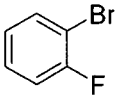
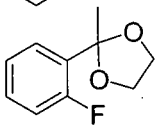
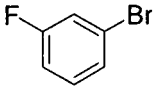
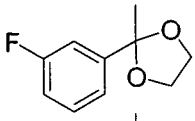
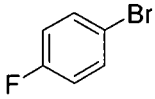
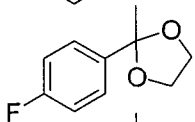
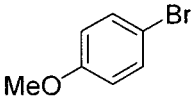
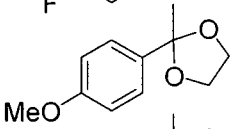
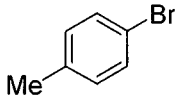
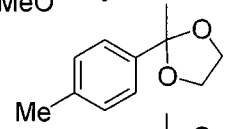
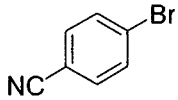
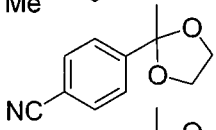
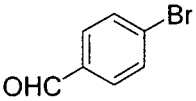
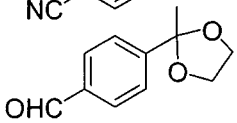
Following on from the inital reaction of **1e** with **2d** and the subesquent solvent study, a range of aryl bromides **2** were screened in the arylation of **1e** in [bmim][BF_4], with all the reactions affording the cyclic ketals that arise from the α arylated **1e**. In a typical reaction, a mixture of **1**, **2**, NEt_3, $Pd(OAc)_2$, and DPPP were heated in [bmim][BF_4] for a certain period of time under an inert atmosphere, and standard work up afforded the product **3**, the results of which are summarised in Table 2. The reactions afforded >99/1 regioselectivity to the branched products with good to excellent yields. Table 2 also features a remarkable 8 h reaction as shown in entry 1, yielding **3ea**.

Entry 4 shows the reaction of bromobenzene to be completed in 18 h, compared to the 144 h reaction reported by Hallberg, Larhed and coworkers, when stoichiometric TlOAc is added. In its absence, they observed a mixture of α– and β-regioisomers in DMF.[192]

Table 2. Regioselective arylation of 2-hydroxy vinyl ether **1e**[a]



2a **1e** **3ea**

Entry	Substrate		Product		Time (h)	Yield
1		**2a**		**3ea**	8	90
2		**2b**		**3eb**	12	72
3		**2d**		**3ed**	22	86
4		**2e**		**3ee**	18	83
5		**2f**		**3ef**	24	96
6		**2g**		**3eg**	24	82
7		**2h**		**3eh**	24	86
8		**2k**		**3ek**	24	89
9		**2n**		**3en**	24	80
10		**2p**		**3ep**	24	94
11		**2q**		**3eq**	18	63

[a]1.0 mmol **2**, 2.0 mmol **1**, 3 mol% $Pd(OAc)_2$, 6 mol% DPPP, and 1.5 mmol NEt_3 in 2 mL [bmim][BF_4] at 115 °C; 100% conversion and >99/1 regioselectivity for all, as determined by ^1H NMR. Isolated yields.

Excellent regioselectivities and good to excellent isolated yields were achieved despite the nature of the substituents on the aryl ring. Bromobenzenes bearing either

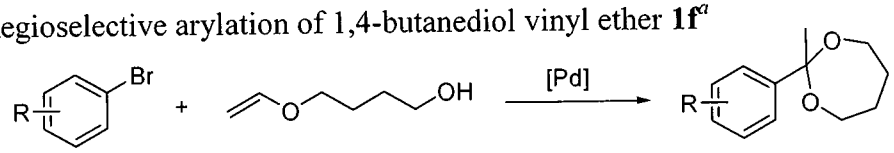
strongly electron-withdrawing (Entries 3, 7, 10-11) or electron-donating substituents (Entries 8 and 9), in the *para* position, all provided good to excellent isolated yields, showing a wide applicability in the range of aryl bromides for this reaction. The *meta* substituent (Entry 5) produced similar results, and even in the sterically hindered *ortho* positions (entry 2 and 5), the reaction worked well, given that the bulky bidentate ligand will be bound to the Pd centre.

No halide scavenger is required here, and the reaction appears to be faster than that reported in literature by Hallberg and coworkers. It is also interesting to point out that the ionic liquid [bmim][BF_4] allows the internal arylated product to cyclise to give **3** with no need for the addition of acid. HOAc is sometimes necessary for the reactions in the conventional solvent.[192] The excellent regioselectivity in [bmim][BF_4] shows that Path B (Scheme 1.09) dominates the reaction, and Path A is completely suppressed, or it is not involved in the arylation in the ionic liquid. What is also worth noting, is that it was not possible to isolate the coupled product before cyclisation, which would indicate that the ketal is in fact the kinetic product.

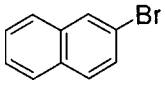
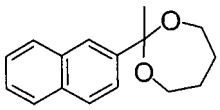
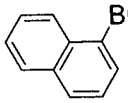
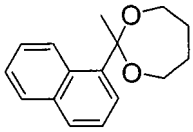
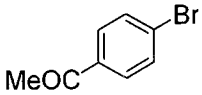
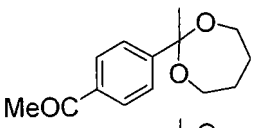
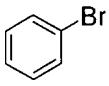
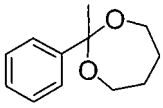
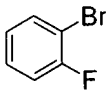
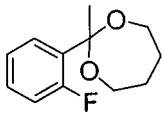
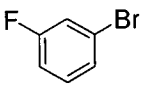
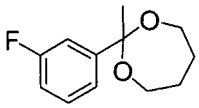
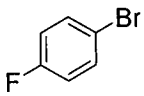
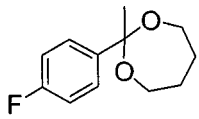
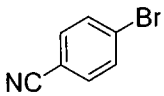
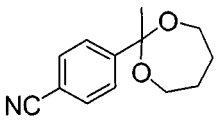
These results led us to expand the scope of the reaction to a different ether, 4-hydoxyl butyl vinyl ether, **1f**, to produce branched 7-membered ketal rings in fair to good yields (61-86%), for the arylation of some of the substrates featured in Table 3. These reactions on the whole required slightly longer reaction times, and were of lower yields then the 5-membered ketals in Table 2. The low yields encountered may be attributed to the relative instability when separated *via* a silica column, leading to ring opening of ketals.

Table 3 illustrates the tolerance of the reaction for many varying functional groups of differing electronic properties. Noteworthy are entries 2 and 5, where the product is sterically hindered by the naphthalene ring and the fluoride, respectively.

Table 3. Regioselective arylation of 1,4-butanediol vinyl ether **1f**[a]



2 **1f** **3**

Entry	Substrate	Product	Time (h)	Yield
1	 **2a**	 **3fa**	24	71
2	 **2b**	 **3fb**	30	77
3	 **2d**	 **3fd**	24	79
4	 **2e**	 **3fe**	24	61
5	 **2f**	 **3ff**	30	75
6	 **2g**	 **3fg**	32	72
7	 **2h**	 **3fh**	24	86
8	 **2p**	 **3fp**	24	76

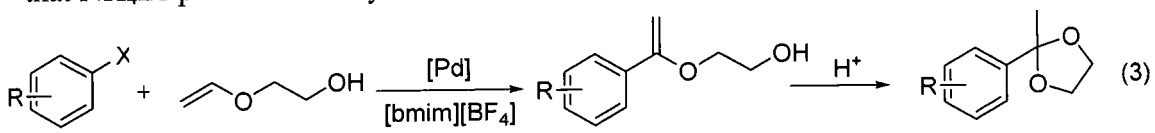
Reaction conditions: [a]1.0 mmol **1**, 2.0 mmol **2b**, 3 mol% $Pd(OAc)_2$, 6 mol% DPPP, and 1.5 mmol NEt_3 in 2 mL [bmim][BF_4] at 115 °C; 100% conversion and >99/1 regioselectivity for all, as determined by ^1H NMR. Isolated yields.

The entries featuring electron-withdrawing groups in the *para* postion to the dissociating bromide (entries 3, 7 and 8) were completed in shorter times than others (entries 2, 5 and 6). Those substrates bearing electron-donating groups were sluggish and could not be successfully arylated in 36 h, and therefore have not been included.

The variation of functional groups on the aryl bromide **2** applied in both reactions shows a wide versatility in a range of different substrates. Aryl groups containing electron withdrawing/donating group *para*, *ortho* or *meta* to the bromide can be applied, with slight variations in reaction time.

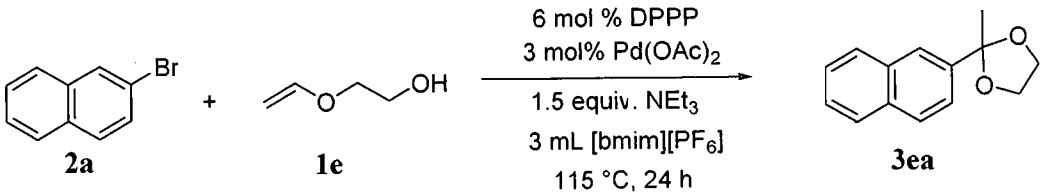
The arylation of **1** by bromide **2** presumably proceeds *via* the cationic pathway B (Scheme 1.09), and we believe that it is the unique ionic property of the ionic liquid that makes this possible. In accordance with the findings made by Hallberg and Larhed,[192] the reaction first leads to the arylation of **1**, giving rise to an α-arylated vinyl ether. This is followed by cyclisation to give the cyclic ketals **3**.

Unlike the reaction in DMF, however, no additional Brönsted acid is needed for the cyclisation in [bmim][BF_4] (Eq. 3). In the latter case, the reaction might be promoted by the ammonium salt $HNEt_3^+$ generated in the Heck coupling step or by the Lewis acidic C^2-H proton of the imidazolium cation. Hallberg and Larhed show that NH_4Br promotes the cyclisation.[192]



(3)

The regioselective Heck arylation of **2a** can also be performed in the ionic liquid [bmim][PF_6]. [bmim][PF_6] is known to readily form a triphasic system of [bmim][PF_6]/H_2O/alkanes with water and non-polar solvents, which makes the catalyst recycling possible.[96] An excess of **1e** was not necessary, however more ionic liquid was used initially. When diethyl ether was used to extract the product, and water to extract the ammonium bromide salt, the catalyst and the ionic liquid [bmim][PF_6] could indeed be recycled and reused for at least 8 times without significant loss of catalytic effect under the chosen condtions (Scheme 2.04).



2a + **1e** → **3ea**

Run	1	2	3	4	5	6	7	8
Yield, %	85	89	84	83	81	86	81	88

Scheme 2.04. Catalyst recycle.

The results show that not only does ionic liquid provide an excellent catalytic system for this reaction, but also the catalyst and solvent can be recycled to give equally good yields and selectivites after each recycle.

2.3. Conclusion

The Heck reaction has advanced to great levels in developing active and productive catalysts, but hampered by the lack of regioselectivity in the intermolecular arylation of electron rich olefins with aryl halides. When the arylation was carried out in molecular solvents a mixture of products was observed, whereas in ionic liquids excellent regioselectivity was obtained, with no sign of the linear product. The reaction of **1e** and **2a** could be completed in 8 h yielding the corresponding 5-membered ketal, compared to 144 h reported by Hallberg and coworkers. This excellent regioselectivity and high yield was maintained in the arylation with a range of aryl bromides (**2b-2p**), and the scope was further extended to the arylation olefin **1f**, again affording excellent regioselectivities and high yields of the 7-membered ketal.

In summary, we have developed an efficient method for the internal arylation of hydroxyalkyl vinyl ethers by aryl bromides by using Pd-DPPP catalysis in the ionic

liquids [bmim][BF_4] and [bmim][PF_6]. The resulting products cyclise *in situ* to give cyclic ketals in good to excellent isolated yields, and the catalyst and ionic liquid can be recycled. The Pd-DPPP catalysis described here is typical of the Heck reaction proceeding *via* the cationic pathway. As a solvent made entirely of ions, the ionic liquid promotes this pathway and hence renders the addition of halide scavengers totally unnecessary. This excellent catalytic system offers remarkable regioselectivity through exclusive substitution by the aryl group, and demonstrates that a series of aryl groups with various electronic and steric properties can be employed. This approach represents a short route to these compounds that would otherwise be difficult to prepare.

2.4. Experimental Section

General

All reactions were carried out under a nitrogen atmosphere. Chromatographic purifications were performed on silica gel (mesh 230-400) by the flash technique. Following vacuum-drying at 80 °C for 8 h, the ionic liquid was stored under nitrogen at ambient temperature. $AgNO_3$ titration showed the chloride content of the ionic liquid to be below detection limit (< 0.2%). ^1H and ^{13}C NMR spectra were recorded on a Gemini 400 spectrometer at 400 (^1H) and 100 MHz (^{13}C) in ppm with reference to TMS internal standard in $CDCl_3$. Mass spectra were obtained by chemical ionisation (CI). All the products were satisfactorily characterised by ^1H and ^{13}C NMR, MS, HRMS and elemental analysis when possible. All spectra were referenced with those that were available in literature. The following compounds, 5-membered ketals, **3ea** [69470-12-8][200], **3eb** [760211-67-4][251], **3ed** [105752-35-0][192], **3ee** [3674-

77-9][288], **3ef** [261966-94-3][251], **3eh** [36881-03-5][200], **3ep** [66522-61-0][289], **3eq** [14490-45-0][251] and 7-membered ketals **3fd** [908121-03-9][251] and **3fe** [143414-17-9][192] have all been reported previously. All reactions were carried out under vacuum and in a nitrogen atmosphere. All glassware involved in the reaction was thouroughly washed, and oven-dried to avoid any moisture or residue. The aryl halides **2a-2q** olefins **1e** and **1f**, $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (DPPP), and triethylamine were purchased from Lancaster and Aldrich and were used as received. All aromatic substrates were obtained from Sigma-Aldrich.

Monitoring the reaction. An initial reaction was carried out using 4-bromoacetophenone **2d** (199mg, 1.0 mmol), and the reaction went to completion after 22 h. A second reaction was then carried out under the same conditions, however small aliquots were extracted from the reaction mixture with a glass syringe every 4 h up to 8 h, then every 2 h until 18 h had elapsed. The aliquots were then dissolved in 1 mL DCM, washed 3 times with water, and dried over $MgSO_4$, and the solvent was then evaporated. ^1H NMR was obtained and against those found in literature. It was found that for this particular aryl bromide, the reaction went to completion after 8 h.

Optimising conditions. For the cyclisations, it was vital to obtain the most efficient reaction using as little catalyst possible. A preliminary reaction was carried out using 4-bromoacetophenone **1d** (199mg, 1.0 mmol), and only 0.01 mmol Pd $(OAc)_2$. The reaction was monitored every 4 h for 12 h, but stopped after 12 h. The reaction had not gone to completion even after 12 h, and starting material was still left unreacted. Therefore, it was decided to use 3 mol% catalyst as previously used, with the advantage of a faster reaction time.

Preparation of ionic liquid. The methods used in literature were applied to prepare the ionic liquid, 1-butyl-3-methylimidizolium tetrafluoroborate ([bmim][BF_4]).[79] The

ionic liquid was vacuum dried at 80°C for 8 h, and stored under nitrogen at ambient temperature after its preparation. The ionic liquid was vacuum-dried again ahead of the application in the reaction, for 1 hour, at 80°C.

Procedure for solvent study (Table 1). This procedure is identical to the isolation of cyclic ketals, ionic liquid was replaced by the corresponding solvent (*vide infra*).

Procedure for preparation of cyclic ketal synthesis (Table 2 and Table 3). The first 3 reactions were initially carried out in an oil bath, under vacuum and a nitrogen atmosphere (Entries 1-3, Table 2). The oil bath is heated to 115 °C, with a probe which was used to maintain the temperature. A magnetic stir bar was placed in the bottom of a Schlenk Tube, with Pd $(OAc)_2$ (6.7mg, 0.03 mmol) and DPPP (24.8mg, 0.06 mmol). The aryl bromide (1.0 mmol) was added, along with the olefin, 2-hydroxyethyl vinyl ether (2.0 mmol) and base triethylamine (1.5 mmol). All liquids were measured and added *via* 1 mL glass syringes, except ionic liquid as it was too viscous, 2 mL of which was added *via* Pasteur pipette. The tube was degassed, purged with nitrogen for a few minutes, and put under vacuum. When the oil bath had reached a temperature of 115°C, the tube was lowered into the oil bath and left for the required time, stirring continuously.

For entries 4-11 in Table 2 and all entries in Table 3, the reactions were carried out under the same conditions, but in a parallel reactor, where Pyrex screw cap tubes were used. Vacuum and nitrogen atmosphere were applied in the same way.

When the reaction was complete, the mixture was left to cool. DCM (10 mL) was added to the tube mixture, and then placed into a 250 mL-separating funnel. The tube was washed out thoroughly with DCM, and poured into the funnel to which 50 mL of deionised water was added to remove the ionic liquid. The funnel was stoppered and shaken vigorously, but also frequently releasing the gas from the tap. The heavy

organic layer was collected (the bottom layer) and the ionic liquid suspended in the water removed (top layer). The aqueous layer containing ionic liquid was washed again with 20 mL DCM, and repeated once more to ensure optimum yield is extracted from the aqueous phase. The resulting organic layers were combined and were dried with magnesium sulfate, and left for an hour.

The solution was drained under vacuum using a sintered filter funnel, and collected into a 100 mL round-bottomed flask. The solvent was evaporated off, and the crude compound collected. It was found that some ketals were unstable when left for long periods of time, so the crude product was suspended in DCM (10 mL). A 2 mL aliquot was isolated from this solution, placed in a small round bottom flask, and the solvent was evaporated off. The product was analysed by ^{1}H NMR.

Separation was achieved by the flash technique using a 100ml column over silica gel (mesh 230-400). Thin-layer chromatography was used to find the correct concentration of eluent, usually a ratio of hexane to ethyl-acetate (10/90). Once this was found for each compound, the column was run and collected in test tubes. TLC confirmed which tubes contained product. Each product was collected in a round-bottom flask, solvent was evaporated and sent for ^{1}H NMR, ^{13}C NMR, MS, HRMS, and elemental analysis.

The recycling of palladium catalyst in the Heck arylation of hydroxyalkyl vinyl ether in ionic liquid. An oven-dried, two-necked round-bottom flask containing a stirring bar was charged with 2-bromonaphthalene **2a** (207mg, 1.0 mmol), $Pd(OAc)_2$ (0.03 mmol), DPPP (0.06 mmol), and [bmim][PF_6] (3 mL) under nitrogen at room temperature. Following degassing three times, 2-hydroxy vinyl ether **1e** (2.0 mmol) and NEt_3 (1.5 mmol) were injected. The flask was placed in an oil bath, and the mixture was stirred and heated at 115 °C. After a reaction time of 24 h, the flask was

removed from the oil bath and cooled to room temperature. The resulting mixture was extracted with diethyl ether (5 × 10 mL), and was washed with water (3 × 10 mL). The recovered catalyst and ionic liquid was dried under vacuum, and was then ready for the next run. The diethyl ether was then washed with water until neutrality, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The cyclic ketal **3ea** was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (10/90) containing 2% (in volume) triethylamine as eluant. The isolated yields of the products from each run are given in Scheme 2.05 of the text.

2.5. Analytical Data

2-Methyl-2-(naphtalen-2-yl)-1,3-dioxolane (3ea) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.97-7.82 (m, 3H), 7.49-7.45 (d, *J* = 6.7 Hz, 2H), 7.60-7.58 (m, 1H), 4.10-4.06 (m, 2H), 3.84-3.79 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 129.0, 128.6, 128.5, 128.2, 128.1, 126.6, 126.5, 124.4, 124.2, 109.4, 65.2, 27.8 Cl-MS *m/z* 215 [$(M + H)^+$, 100]; HRMS Calc for $C_{14}H_{15}O_2$ $(M + H)^+$: 215.1072. Found: 215.1074. Anal. Calcd for $C_{14}H_{15}O_2$: C, 78.48, H, 6.59. Found: C, 78.78, H, 6.54.

2-Methyl-2-(naphthalen-1-yl)-1,3-dioxolane (3eb) ^{1}H N MR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.51-7.36 (m, 4H), 4.07-4.03 (m, 2H), 3.80-3.74 (m, 2H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 130.8, 130.7, 129.1, 127.8, 126.4, 126.2, 125.3, 124.1, 123.8, 110.1, 64.7, 27.9 Cl-MS m/z 215 [$(M + H)^+$, 100]; HRMS Calc for $C_{14}H_{15}O_2$ $(M + H)^+$: 215.1072. Found: 215.1076. Anal. Calcd for $C_{14}H_{15}O_2$: C, 78.48, H, 6.59. Found: C, 78.25, H, 6.61.

1-(4-(2-Methyl-1,3-dioxolan-2-yl)phenyl)ethanone (3ed) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.93 (d, *J* = 4.7 Hz, 2H), 7.59-7.57 (d, *J* = 4.7 Hz, 2H), 4.08-4.02 (m, 2H), 3.80-3.72 (m, 2H), 2.61 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 149.0, 137.2, 128.8, 126.0, 108.9, 65.0, 27.8, 27.0 Cl-MS *m/z* 207 [$(M + H)^+$, 100]; HRMS Calc for $C_{12}H_{15}O_3$ $(M + H)^+$: 207.1021. Found: 207.1029. Anal. Calcd for $C_{12}H_{15}O_3$: C, 75.00, H, 6.82. Found: C, 75.26, H, 6.42.

2-Methyl-2-phenyl-1,3-dioxolane (3ee) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 4.8 Hz, 2H), 7.36-7.25 (m, 3H), 4.04 (m, 2H), 3.78 (m, 2H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 128.5, 128.2, 125.6, 109.2, 64.8, 28.0 Cl-MS *m/z* 165

[$(M + H)^+$, 100]; HRMS Calc for $C_{10}H_{13}O_2$ $(M + H)^+$: 165.0916. Found: 165.0916. Anal. Calcd for $C_{10}H_{13}O_2$: C, 73.20, H, 7.37. Found: C, 72.80, H, 7.31.

2-(2-Fluorophenyl)-2-methyl-1,3-dioxolane (3ef) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.48 (m, 1H), 7.29-7.27 (m, 1H), 7.12-7.05 (m, 2H), 4.11-4.03 (m, 2H), 3.89-3.80 (m, 2H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (d, J_{CF} = 246 Hz), 143.8, 130.3 (d, J_{CF} = 16 Hz), 128.1 (d, J_{CF} = 4 Hz), 124.4 (d, J_{CF} = 4 Hz), 117.2 (d, J_{CF} = 22 Hz), 108.2 (d, J_{CF} = 3 Hz), 64.8, 27.8; Cl-MS *m/z* 183 [$(M + H)^+$, 100]; HRMS Calc for $C_{10}H_{12}O_2F$ $(M + H)^+$: 183.0821. Found: 183.0822. Anal. Calcd for $C_{10}H_{12}O_2F$: C, 65.92, H, 6.09. Found: C, 65.96, H, 6.09.

2-(3-Fluorophenyl)-2-methyl-1,3-dioxolane (3eg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (m, 3H), 7.21-717 (m, 1H), 4.05-3.98 (m, 2H), 3.81-3.72 (m, 2H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J_{CF} = 246 Hz), 146.7 (d, J_{CF} = 6 Hz), 130.1 (d, J_{CF} = 8 Hz), 121.2 (d, J_{CF} = 3 Hz), 114.9 (d, J_{CF} = 22 Hz), 112.8 (d, J_{CF} = 22 Hz), 108.6, 64.8, 27.8; Cl-MS *m/z* 183 [$(M + H)^+$, 100]; HRMS Calc for $C_{10}H_{12}O_2F$ $(M + H)^+$: 183.0821 Found: 183.0823. Anal. Calcd for $C_{10}H_{12}O_2F$: C, 65.92, H, 6.09. Found: C, 65.82, H, 6.11.

2-(4-Fluorophenyl)-2-methyl-1,3-dioxolane (3eh) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.42 (m, 2H), 7.02-7.00 (m, 2H), 4.06-4.01 (m, 2H), 3.81-3.74 (m, 2H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J_{CF} = 246 Hz), 140.1 (d, J_{CF} = 3 Hz), 127.5 (d, J_{CF} = 8 Hz), 115.2 (d, J_{CF} = 21 Hz), 100.0, 64.8, 28.5 Cl-MS *m/z* 183 [$(M + H)^+$, 100]; HRMS Calc for $C_{10}H_{12}O_2F$ $(M + H)^+$: 183.0821. Found: 183.0823. Anal. Calcd for $C_{10}H_{12}O_2F$: C, 65.92, H, 6.09. Found: C, 65.96, H, 6.09.

2-(4-Methoxyphenyl)-2-methyl-1,3-dioxolane (3ek) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (d, J = 4.6 Hz, 2H), 6.87-6.83 (d, J = 4.6 Hz, 2H), 4.01-3.98 (m, 2H), 3.77 (s, 3H), 3.76-3.74 (s, 2H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 136.0,

126.9, 114.3, 109.1, 64.7, 55.5, 27.8; Cl-MS *m/z* 195 [(M + H)$^+$, 100]; HRMS Calc for $C_{11}H_{15}O_3$ (M + H)$^+$: 195.1021. Found: 195.1020. Anal. Calcd for $C_{11}H_{15}O_3$: C, 68.00, H, 7.27. Found: C, 68.01, H, 7.25.

2-Methyl-2-*p*-tolyl-1,3-dioxolane (3en) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (d, *J* = 4.8 Hz, 2H), 7.15-7.13 (d, , *J* = 4.8. Hz, 2H), 4.03-3.99 (m, 2H), 3.78-3.75 (m, 2H), 2.33 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 137.8, 128.8, 125.6, 109.3, 64.8, 32.0, 27.8; Cl-MS *m/z* 179 [(M + H)$^+$, 100]; HRMS Calc for $C_{11}H_{15}O_2$ (M + H)$^+$: 179.1072. Found: 179.1073. Anal. Calcd for $C_{11}H_{15}O_2$: C, 74.10, H, 7.92. Found: C, 74.04, H, 7.90.

4-(2-Methyl-[1,3]dioxolan-2-yl)benzonitrile (3ep) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.51 (m, 4H), 4.01-3.97 (m, 2H), 3.70-3.66 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 131.2, 125.2, 117.7, 110.8, 107.2, 63.7, 26.6; Cl-MS *m/z* 207 [(M + NH_4)$^+$, 100], 190 [(M + H)$^+$, 40]; HRMS Calc for $C_{11}H_{12}NO_2$ (M + H)$^+$: 190.0868. Found: 190.0869. Anal. Calcd for $C_{11}H_{12}NO_2$: C, 69.84, H, 5.82, N, 7.41. Found C, 69.64, H, 5.85, N, 7.33.

4-(2-Methyl-1,3-dioxolan-2-yl)benzaldehyde (3eq) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.89-7.87 (d, *J* = 8.1 Hz, 2H), 7.67-7.65 (d, *J* = 8.3 Hz, 2H), 4.09-4.05 (m, 2H), 3.80-3.75 (m, 2H), 1.67 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 150.5, 136.4, 130.4, 126.4, 108.8, 65.0, 27.8 Cl-MS *m/z* 210 [(M + NH_4)$^+$, 80] 193 [(M + H)$^+$, 100]; HRMS Calc for $C_{11}H_{13}O_3$ (M + H)$^+$: 193.0865. Found: 193.0869. Anal. Calcd for $C_{11}H_{13}O_3$: C, 68.74, H, 6.29. Found: C, 68.45, H, 6.38.

2-Methyl-2-(napthalen-2-yl)-1,3-dioxepane (3fa) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.87-7.81 (m, 3H), 7.63 (d, *J* = 6.8, 1H), 7.47-7.44 (m, 2H), 3.86-3.82 (m, 2H), 3.68-3.63 (m, 2H), 1.71-1.62 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 133.5, 133.2, 128.8, 128.4, 128.2, 127.9, 126.3, 125.2, 124.7, 103.1,

63.6, 29.9, 27.8; Cl-MS *m/z* 243 [(M + H)$^+$, 100]; HRMS Calc for $C_{16}H_{19}O_2$ (M + H)$^+$: 243.1385. Found 243.1387. Anal. Calcd for $C_{16}H_{19}O_2$: C, 79.31, H, 7.49. Found: C, 78.88, H, 7.64.

2-Methyl-2-(naphthalen-1-yl)-1,3-dioxepane (3fb) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.6, 1H), 7.77 (d, *J* = 4.8 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 1H) 7.47-7.40 (m, 3H), 3.91-3.86 (m, 2H), 3.72-3.67 (m, 2H), 1.71-1.62 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 135.5, 131.5, 129.7, 129.6, 127.5, 126.8, 126.0, 125.8, 125.7, 104.3, 64.0, 30.4, 27.5; Cl-MS *m/z* 243 [(M + H)$^+$, 100]; HRMS Calc for $C_{16}H_{19}O_2$ (M + H)$^+$: 243.1385. Found 243.1385. Anal. Calcd for $C_{16}H_{19}O_2$: C, 79.31, H, 7.49. Found: C, 78.88, H, 7.43.

1-(4-(2-Methyl-1,3-dioxepan-2-yl)phenyl)ethanone (3fd) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 6.7 Hz, 2H), 7.55 (d, *J* = 6.7 Hz, 2H), 3.74-3.70 (m, 2H), 3.52-3.48 (m, 2H) , 2.52 (s, 3H), 1.62-1.56 (m, 4H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 150.3, 136.7, 128.6, 126.6, 102.8, 63.7, 29.8, 27.6, 27.1; CI-MS *m/z* 235 [(M + H)$^+$, 100]; HRMS Calcd for $C_{14}H_{19}O_3$ (M + H)$^+$: 235.1334. Found: 235.1328; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.07; H, 7.80.

2-Methyl-2-phenyl-1,3-dioxepane (3fe) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.35-7.31 (m, 2H), 7.28-7.26 (m, 1H), 3.82-3.78 (m, 2H), 3.62-3:59 (m, 2H), 1.68-1.63 (m, 2H), 1.62-1.57 (m, 2H) and 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 128.3, 127.7, 126.2, 103.0, 63.5, 29.9, 27.8; CI-MS *m/z* 193 [(M + H)$^+$, 100]; HRMS Calcd for $C_{12}H_{17}O_2$ (M + H)$^+$: 193.1229. Found: 193.1224; Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.67; H, 8.34.

2-(2-Fluorophenyl)-2-methyl-1,3-dioxepane (3ff) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.43 (m, 1H), 7.28-7.26 (m, 1H), 7.13-7.04 (m, 2H), 3.86-3.81 (m, 2H), 3.66-

3.63 (m, 2H), 1.61-1.51 (m, 4H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (d, J_{CF} = 248 Hz), 131.1(d, J_{CF} = 21 Hz) , 129.8 (d, J_{CF} = 8 Hz), 128.9 (d, J_{CF} = 4 Hz), 123.7 (d, J_{CF} = 3 Hz), 116.8 (d, J_{CF} = 23 Hz), 101.5, 63.5, 30.8, 29.8; Cl-MS *m/z* 211 [$(M + H)^+$, 100]; HRMS Calc for $C_{12}H_{15}FO_2$ $(M + H)^+$: 211.1134. Found 211.1136; Anal. Calcd for $C_{12}H_{15}FO_2$: C, 68.55, H, 7.19. Found: C, 68.33, H, 7.18.

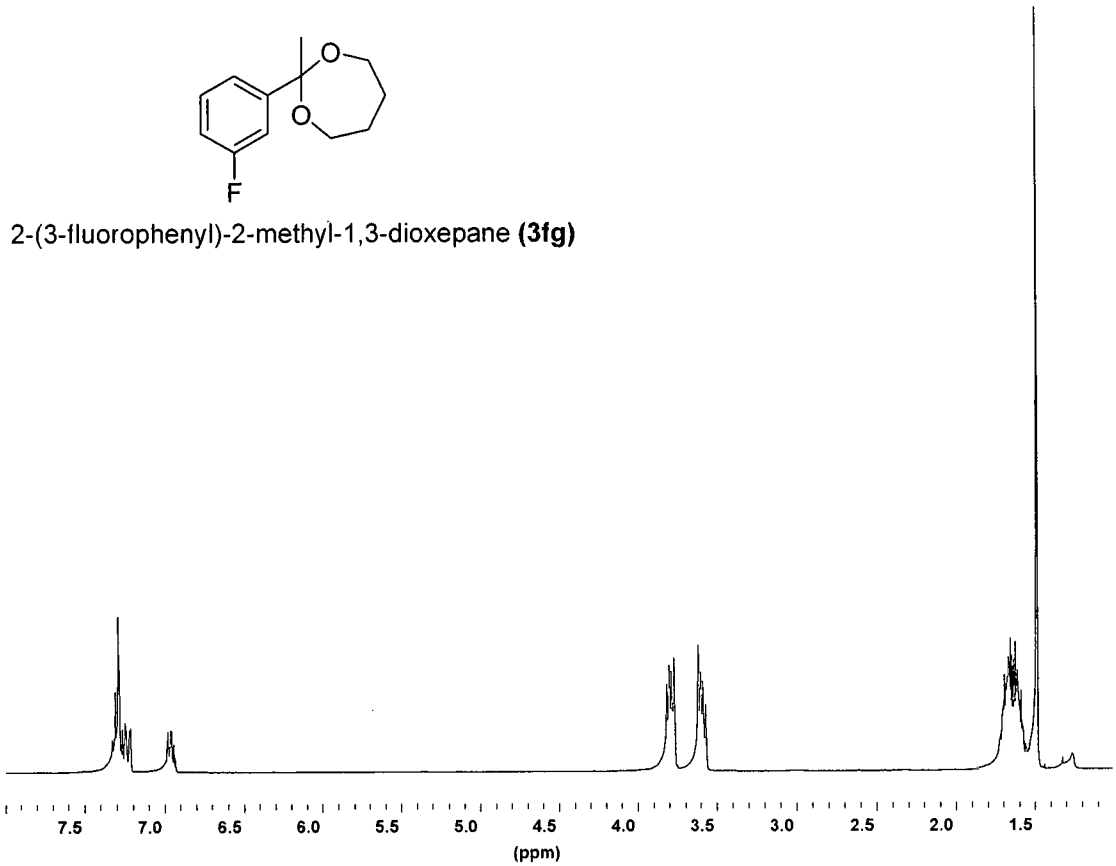
2-(3-Fluorophenyl)-2-methyl-1,3-dioxepane (3fg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.23 (m, 3H), 7.81-7.89 (m, 1H), 3.74-3.69 (m, 2H), 3.54-3.49 (m, 2H), 1.61-1.51 (m, 4H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J_{CF} = 245 Hz), 148.0 (d, J_{CF} = 8 Hz), 129.9 (d, J_{CF} = 8 Hz), 121.9 (d, J_{CF} = 3 Hz), 114.5 (d, J_{CF} = 21 Hz), 113.5 (J_{CF} = 23 Hz), 102.6, 63.6, 29.8, 27.7; Cl-MS *m/z* 211 [$(M + H)^+$, 100]; HRMS Calc for $C_{12}H_{15}FO_2$ $(M + H)^+$: 211.1134. Found 211.1140. Anal. Calcd for $C_{12}H_{15}FO_2$: C, 68.55, H, 7.19. Found: C, 68.48, H, 7.20.

2-(4-Fluorophenyl)-2-methyl-1,3-dioxepane (3fh) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.98 (m, 1H), 7.50-7.44 (m,1H), 7.03-6.95 (m, 2H), 3.80-3.75 (m, 2H), 3.62-3.55 (m, 2H), 1.69-1.60 (m, 4H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, J_{CF} = 243 Hz), 131.8, 128.5 (d, J_{CF} = 8 Hz), 117.4 (d, J_{CF} = 3 Hz), 115.5 (d, J_{CF} = 21 Hz), 63.9, 30.3, 28.3. Cl-MS *m/z* 211 [$(M + H)^+$, 100]; HRMS Calc for $C_{12}H_{16}FO_2$ $(M + H)^+$: 211.113. Found 211.114. Anal. Calcd for $C_{12}H_{15}FO_2$: C, 68.55; H, 7.19. Found: C, 68.73; H, 7.21.

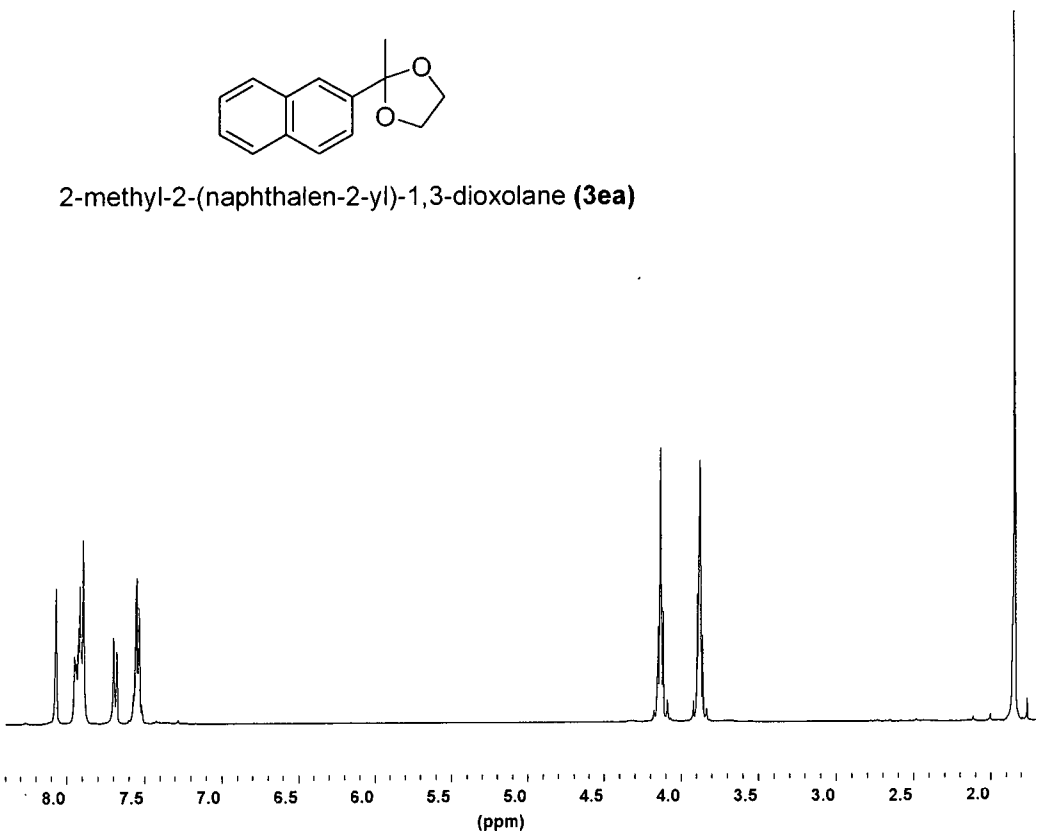
4-(2-Methyl-1,3-dioxepane-2-yl)benzonitrile (3fp) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 4H), 3.82-3.78 (m, 2H), 3.58-3.54 (m, 2H), 1.70-1.61 (m, 4H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 132.4, 127.2, 119.3, 111.7, 102.5, 63.8, 29.7, 27.6; Cl-MS m/z 218 [$(M + H)^+$, 100]; HRMS Calc for $C_{13}H_{16}NO_2$ $(M + H)^+$: 218.1181. Found 218.1183. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.44. Found: C, 71.99; H, 7.03; N, 6.39.

2.6. H^1 NMR Sample Spectra

2-(3-fluorophenyl)-2-methyl-1,3-dioxepane **(3fg)**



2-methyl-2-(naphthalen-2-yl)-1,3-dioxolane **(3ea)**



CHAPTER THREE

No halide scavengers, No Ionic additives: A Greener Regioselective Heck Arylation

3.1. Introduction

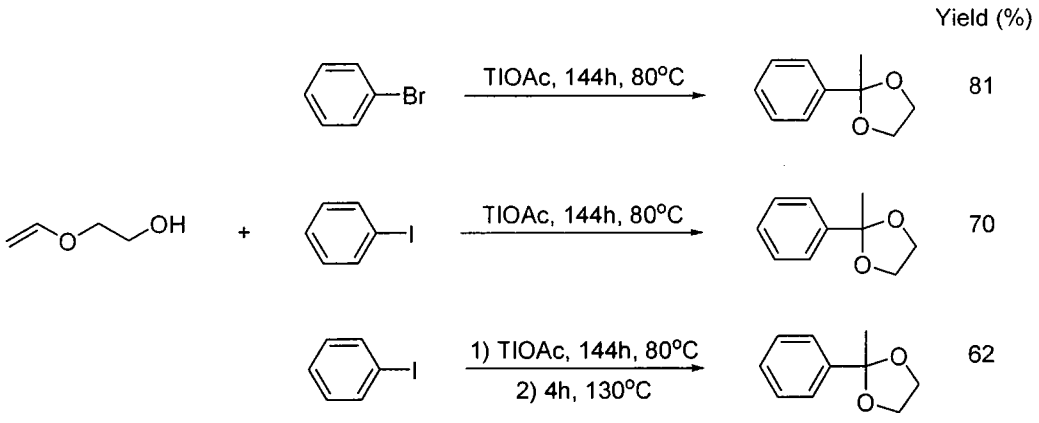
The formation of new sp^2 C-C bonds through the palladium-catalysed Heck reaction is one of the most important tools in synthetic chemistry.[21,152,175,177,290,291] However, a regioselectivity issue exists when electron-rich olefins are employed, which give rise to a mixture of α- and β-regioisomers, due to the operation of two reaction pathways (1.09).[21,151,175,181,182,238]

Extensive research by the groups of Cabri,[151,181,182,238] Hallberg and Larhed,[175,190-192,197,250,292,293] and others[187-189,250,294-296] has established two methods to deal with this problem: 1) when aryl halides are the substrates, addition of stoichiometric amounts of silver or thallium salts, and 2) use of aryl/vinyl triflates instead of the halides.[253,263,297-300] These conditions promote the ionic pathway A and so the α product (Scheme 1.09).[157,158, 240,243] However, silver introduces added cost, whereas thallium salts are toxic, and triflates are generally commercially unavailable, base sensitive, and thermally labile. When these methods are applied to intermolecular arylation, they generally afford low TONs and TOFs, some reactions requiring exceedingly long times and high catalyst loadings.

Pioneering work by Cabri and coworkers in this area exposed many aspects of the reaction of electron-rich olefins which were unknown, and this insight into the mechanism revealed a scope which was previously found to be limited. They tested a series of palladium catalysed reactions between butyl vinyl ether and naphthyl

derivatives to investigate the effect of leaving group and salt additive effects. Selectivity towards the branched product was favoured when bidentate ligands were chosen in the Heck coupling of aryl triflates and the electron rich olefin butyl vinyl ether. When arylbromides were employed, and stoichiometric amounts of TlOAc were added, the internal product was exclusively formed in times of 0.8-12 h, at a palladium loading of 2.5-5.5 mol%, whereas for aryl iodides, times varied from 0.7-24 h. When AgOTf was added to the arylbromide, times of 18-24 h were required for full conversion to the branched product.[151,181,182,238]

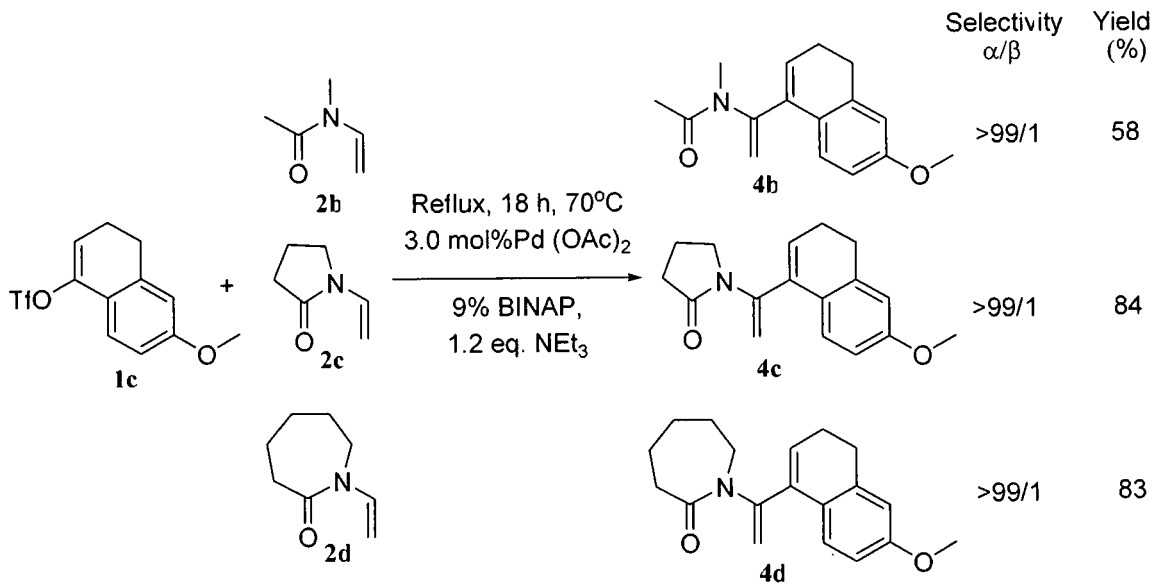
Thallium salts were used by Hallberg and coworkers in the coupling of electron rich hydroxyalkyl vinyl ether with bromo- and iodobenzene, and for some substrates up to 144 h reaction time was necessary to complete (Scheme 3.01). The reaction was carried out in DMF, with a $Pd(OAc)_2$-DPPP catalyst system at a 3 mol% Pd loading, and they obtained selective α-arylations to give the corresponding aryl vinyl ethers, which underwent subsequent ketalisation to form the 5-membered cyclic rings depicted in Scheme 3.01.[192]



Scheme 3.01. Palladium-catalysed regioselective synthesis of cyclic ketals from aryl halides using thallium salts.

The β-arylation was achieved by Santelli and coworkers who applied the same hydroxyether to aryl bromides in DMF, using their tetrakis(phosphane) ligand, Tedicyp (also, see Chapter 5).[301] However, exclusive regioselectivity toward the linear ketal was not achieved.[251]

When triflates are used, reaction times may vary depending on the coupling partner. For example, Skrydstrup and coworkers reported the coupling of the commercially unavailable *N*-acyl-*N*-vinylamines with aryl triflates to produce *N*-acyl-α-arylvinylamines of potentially high synthetic value and versatility. Good yields with short reaction times (under 2 h) were achieved, without competing amidations, with >19:1 branched to linear product selectivity (Scheme 3.02).[188] The Heck coupled products easily underwent acid hydrolysis to the corresponding ketone, or *in situ* hydrogenation in the presence of $(Ph_3P)_3RhCl$ under a hydrogen atmosphere to provide the *N*-acyl derivatives of pharmaceutically relevant benzylic amines.



Scheme 3.02. Heck vinylation of enamides with aryl triflates.

Vallin and coworkers tested a series of reactions on similar electron-rich olefins with vinyl triflates.[190] Under different catalytic systems, the selective vinylic substitution of the α-hydrogen of three different *N*-alkylated enamides was attained. The reaction required overnight heating, followed by a short session of microwave heating to reduce homocoupling products (15-30 min), affording good selectivity and moderate to fair yields. The best selectivities were achieved when using 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (*rac*-BINAP), improving yields and reducing by-product formation, rather than using DPPP. Excellent results were accomplished in the reaction of naphthyl triflates and butyl vinyl ether, using DPPP as ligand, yielding exclusively the branched α-product at 100% conversion in 5 h. The high selectivity, simplicity, and generality of the experimental procedure makes the approach to 2-acylamino-1,3-butadienes and aryl ketones very attractive in organic synthesis, even though reaction times varied.[190]

Combined with a greater need to operate using greener or potentially green solvents for improving organic synthesis to be more environmentally benign, the past few years have seen the coupling of aryl halides executed in imidazolium ionic liquids as solvents, and allowing a degree of regiocontrol (also, see Chapter 1 and 2).[100,246] The Xiao group reported the use of ionic liquids with the readily available $Pd(OAc)_2$ and DPPP, implementing extremely high regiocontrol in the arylation of electron rich olefins by aryl halides thus circumventing the need for silver or thallium additives.[103-105,107,110,199,201,220,295] However, ionic liquids can often be laborious to synthesis, requiring long times and expensive starting materials (Aldrich costs [bmim][BF_4] at £95.60/5g). Little is known regarding toxicity of many imidazolium based ionic liquids.[225-229] Although ionic liquids are unlikely to contribute to air pollution, their potential effects on aquatic ecosystems are largely debated, and how ionic liquids will

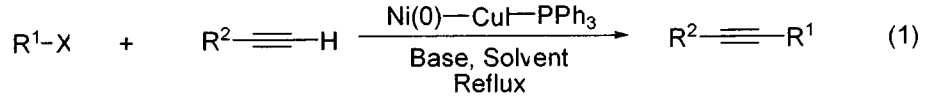
interact with common features of aquatic environments, such as dissolved organic matter (DOM) .[302]

Following on from our study, we reported that high regiocontrol was possible in common organic solvents, promoted by a hydrogen-bond donating salt.[200] This ammonium salt has the potential to not only induce the pathways in favour of the ionic route (Scheme 1.09), but also has the ability to greatly accelerate the reaction using a Pd-DPPP catalytic system, producing TONs and TOFs that have never been seen before in this area of chemistry.[200] Our ventures allowed the Heck reaction to proceed with no requirement for aryl triflates or halide scavengers. Under these conditions, the key cationic Pd(II) species in pathway A is favoured, enhancing the selectivity for the α product.[107,200] Recent studies by Amatore, Jutand and coworkers support this view.[157,158] However, the method necessitates a large quantity of expensive imidazolium or ammonium salts.

In continuing our search for a better regioselective Heck reaction, we report in this chapter that the Heck arylation of aryl halides with electron-rich olefins can be most easily performed *in alcohols*, in a highly regioselective and efficient manner with no need for any salt or ionic additives. Alcoholic solvents provide an attractive cheap alternative to organic solvents traditionally used in catalytic processes, in which a great deal of safety, health and environmental issues arise. This is chiefly due to their flammability, toxicity and volatility, so sustainable chemical processes are being increasingly sought making use of more benign media (also see Chapter 1, section 1.2). Despite the advantages of alcohols, they have been seldom exploited in metal-catalysed coupling reactions.[100,210-214,216,303,304]

One such example is the Sonogashira coupling of terminal acetylenes with aryl or vinyl halides, usually catalysed by palladium, which is one of the most common

methods of synthesis for terminal and internal alkynes.[210] Zhang and coworkers have achieved the coupling reaction of terminal alkynes with aryl iodides, vinyl iodides and aryl bromides in heterogeneous catalytic conditions using ultrafine nickel(0) particles, where the cheaper and extremely catalytically active ultrafine Ni(0) catalyst can be recycled without change of activity (Eq. 1).

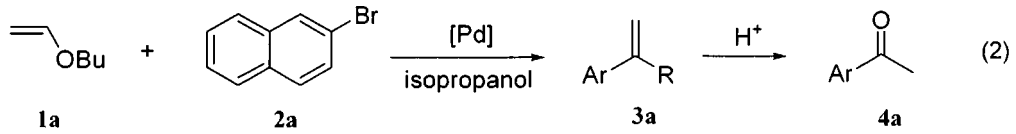


In a series of optimisation reactions in the coupling of phenylacetylene and *p*-iodotoluene, with potassium hydroxide as a base, it was found that the reaction carried out in isopropanol achieved an extremely high yield of product of 98%, excelling over the more commonly employed organic solvents such as DMSO and DMF (58% and 80%, respectively). After optimisation, an isopropanol/KOH system was chosen; aromatic terminal alkynes and aliphatic terminal alkynes were successfully coupled with aromatic, heteroaromatic and vinyl iodides in moderate to good yields. Aryl bromides with terminal alkynes formed only moderate to good yields (56-63%) of the coupled product under the unoptimised reaction conditions (a DMF/K_2CO_3 mixture). Substituent effects of aromatic terminal alkynes and aromatic iodides were examined, and indicated that the reaction is tolerant of electronic characteristics of the substituents as well as its location.[210]

Very recently, Larhed and coworkers reported that water can be used as solvent for fast, highly regioselective arylation.[218,223] However, the chemistry appears to be restricted to hydroxyl vinyl ethers (also, see Chapter 4)

Alcohols are good hydrogen bond donors and are known to act as receptors for halide anions.[305,306] This feature can aid the dissociation of halide anion from Pd(II),

thereby enhancing the concentration of the ionic Pd(II)-olefin species in pathway A (Scheme 1.09).[200,223,251,307,308] Short chain alcohols are also known to have hydrogen bond donating capabilities similar to imidazolium ionic liquids.[309-312] With this in mind, we set out to investigate whether the regioselective Heck arylation of electron-rich olefins could be affected in a simple alcohol like isopropanol (Eq. 2).



1a **2a** **3a** **4a** (2)

Unlike ionic liquids in which long-standing research in the field is lacking, and little is known about long-term effects of exposure, it is important to understand the benefits of alcohols such as isopropanol in terms of sustainability. Over the past two decades, the drive for more sustainable products and processes has triggered the (further) development of a number of assessment tools which measure environmental impact of a particular solvent, from its production, through to its use and finally, disposal. One paper utilises three methods which may be applied in the synthesis of chemical products and the development of chemical processes; namely, one screening tool for assessing environmental, health, and safety hazards (EHS), one tool for product assessment using persistence and spatial range (PSR) as indicators, and life-cycle assessment (LCA).

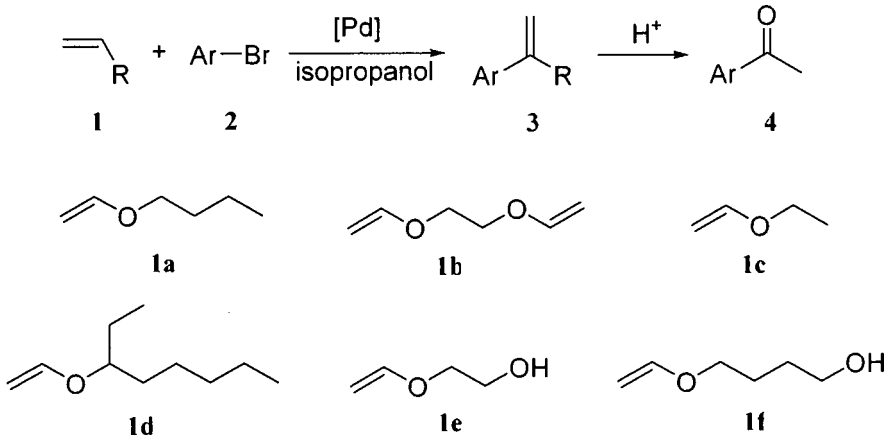
The EHS method assesses eleven effect categories: mobility of the chemical at room temperature, fire/explosion, reaction/decomposition, acute toxicity, chronic toxicity, irritation, air mediated effects, water mediated effects, solid waste, accumulation and degradation.[313] PSR or characteristic travel distance are indicators used to describe the exposure potential of chemicals, with respect to persistence and spatial range which identifies potential contributions to long-lasting and wide-spread

exposure after the chemical is released at a certain point. [314,315] LCA is used to study the environmental impacts throughout a product's life, from the raw material through production, to its use and disposal *i.e.* from cradle to grave, and is used to identify environmental improvement potentials along the life-cycle of the product. In a study by Hellweg and coworkers,[316] a large series of solvents were tested ranging from halogenated, organic and alcohol solvents, chosen for their widespread use and total production on a global scale.

In terms of EHS, isopropanol and methanol were shown to be the least hazardous to health, public safety and to the environment. The spatial range for isopropanol recorded a persistence of around 10 days (examined measuring the solvents half-lives in water, soil and air), but a spatial range below 10% representing no or very little potential for widespread and long-lasting exposure (to compare, chlorinated solvents have a persistence of 100 days, and an extremely high spatial range of 55%). The results indicate that chlorinated solvents and nitrobenzene, if released in significant quantities, can cause long-lasting and widespread exposure. The LCA is a complex tool; its applicability is dependent on many factors, which can be culminated into one method of analysis called Eco-indicator 99, which takes into account respiratory effects, and direct solvent emissions such as SO_x, NO_x. Isopropanol and methanol again have the lowest Eco-indicator, and trace human toxicity.[314,316]

As good alternatives to chlorinated or organic solvents, we decided to apply alcohols to the Heck reaction. In this chapter we report the first regioselective arylation of electron rich olefins with aryl bromides *in isopropanol* (Scheme 3.03). Isopropyl alcohol is produced by combining water and propene.[317] There are two processes for achieving this: indirect hydration via the sulfuric acid process and direct hydration. The former process, which can use low-quality propylene, predominates in

the USA while the latter process, which requires high-purity propylene, is more commonly used in Europe. These processes give predominantly isopropyl alcohol rather than 1-propanol because the addition of water or sulfuric acid to propylene follows Markovnikov's rule.[318] The indirect process reacts propylene with sulfuric acid to form a mixture of sulfate esters. Subsequent hydrolysis of these esters produces isopropyl alcohol. Direct hydration reacts propylene and water, either in gas or liquid phases, at high pressures in the presence of solid or supported acidic catalysts. Both processes require that the isopropyl alcohol be separated from water and other by-products by distillation.



Scheme 3.03. Regioselective arylation of electron-rich olefins **1a-f** in isopropanol.

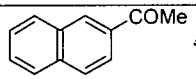
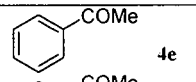
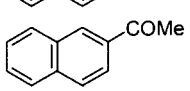
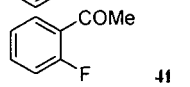
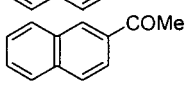
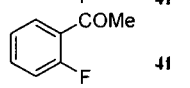
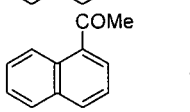
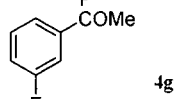
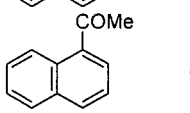
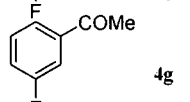
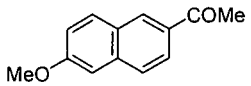
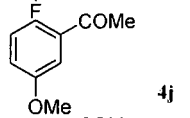
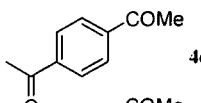
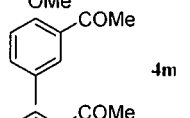
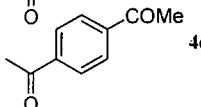
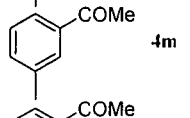
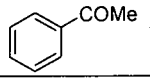
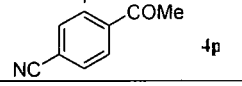
3.2. Results and Discussion

We first examined the feasibility in the arylation of butyl vinyl ether **1a** with 2-bromonapthalene **2a** under Pd-DPPP catalysis. Remarkably, the arylation of **1a** with **2a** completed in 5 h with no linear product detected; the ketone **4a** was isolated after acidification of **3a** in excellent yield (Table 1, Entry 1). A variety of other aryl bromides **2b-p** were then tested with a range of alkyl vinyl ethers **1a-d**.

In a typical reaction, a mixture of **1**, **2**, $Pd(OAc)_2$, DPPP and triethylamine was heated in 2 mL isopropanol under reflux in an inert atmosphere of N_2; the ketone was

obtained following hydrolysis of **3**. As can be seen in Table 1, good to excellent yields were obtained for all the reactions, and in no case was the linear olefin detected or isolated. Apart from entry 1, all reactions required between 8-18hrs reaction time, and it was found that aryl bromides which had –OMe and –Me *para* to the bromide could not be arylated within 24 h, indicating that oxidative addition is probably affected by strongly electron-donating substituents. Sterically hindered aryl **2b** could also be arylated with ease (Entry 4 and 5) butyl vinyl ether **1a**, and the divinyl ether **1b**. Entry 18 shows the successful arylation of **1a** by **2p** which contains a strongly electron withdrawing group *para* to the bromide.

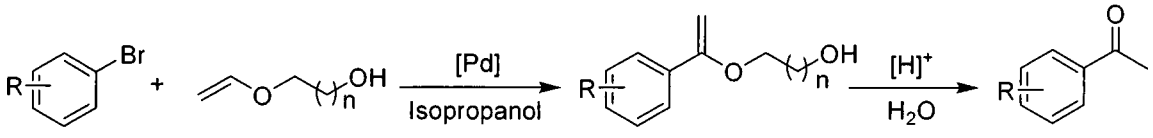
Table 1. Regioselective arylation of olefins **1** in isopropanol[a]

Entry	Olefin	ArBr	Product	Yld (%)	Entry	Olefin	ArBr	Product	Yld (%)
1[b]	1a	2a	 4a	92	10	1d	2e	 4e	81
2[b]	1b	2a	 4a	78	11	1d	2f	 4f	76
3	1c	2a	 4a	82	12	1c	2f	 4f	72
4	1a	2b	 4b	88	13	1a	2g	 4g	78
5[c]	1b	2b	 4b	87	14[c]	1b	2g	 4g	77
6	1a	2c	 4c	75	15	1a	2j	 4j	87
7[c]	1b	2d	 4d	81	16[c]	1b	2m	 4m	84
8	1c	2d	 4d	79	17	1c	2m	 4m	85
9	1a	2e	 4e	87	18	1a	2p	 4p	83

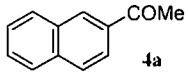
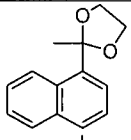
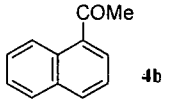
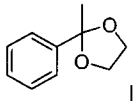
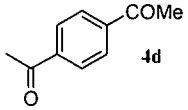
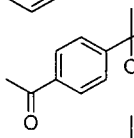
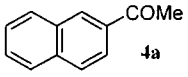
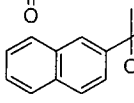
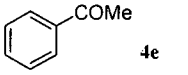
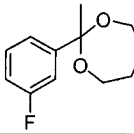
[a]Reaction conditions: **1** (3.0 equiv), **2** (1.0 mmol), Pd $(OAc)_2$ (5.0 mol%), DPPP (10.0 mol%), NEt_3 (2.5 equiv.) and *i*PrOH (2 mL) at 115 °C, for 18–24 h; 100% conversion and no linear products, as shown by 1H NMR analysis; isolated yields are reported; 4 was obtained after acidification of 3. [b]5 h reaction time. [c]0.75 equiv. 1b.

From our studies in ionic liquid, we found that arylation of hydroxyl ethyl vinyl ethers **1e** and **1f** could be successfully arylated, and form 5- and 7-membered ketals without the need for further acidification to complete ring closing (also, see Chapter 2). We then attempted to expand the scope of olefin to hydroxyl vinyl ethers **1e** and **1f** in isopropanol. Selected examples are included in Table 2.

Table 2. Regioselective arylation of olefins **1e** and **1f** in isopropanol[a]



2 1e-f 3 4

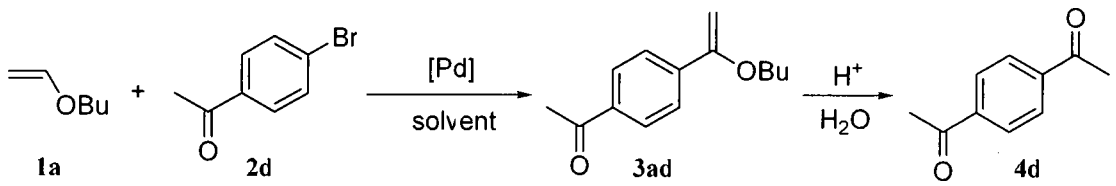
Entry	Olefin	ArBr	Product	Yld (%)	Entry	Olefin	ArBr	Product	Yld (%)
1	1e	2a	 4a	78	6[b]	1e	2b	 3eb	82
2	1e	2b	 4b	84	7[b]	1e	2e	 3ee	87
3	1e	2d	 4d	89	8[b]	1e	2d	 3ed	85
4	1f	2a	 4a	86	9[b]	1f	2a	 3fa	83
5	1f	2e	 4e	78	10[b]	1f	2g	 3fg	89

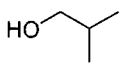
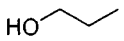
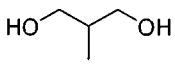
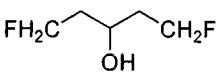
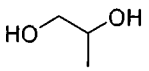
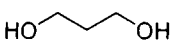
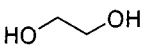
[a]Reaction conditions: **1** (3.0 equiv), **2** (1.0 mmol), Pd $(OAc)_2$ (5.0 mol%), DPPP (10.0 mol%) and NEt_3 (2.5 equiv) in isopropanol (2 mL) at 115 °C; 100% conversion and no linear products; isolated yields are reported; **4** was obtained after acidification of **3**. [b]Conditions were the same as for [*a*], omitting aqueous acidic work up (see Chapter 2).

Entries 1-5 demonstrate that arylation can occur with different functional groups on the aryl ring to produce the corresponding ketones, and were completed within 18 h but interestingly, without hydrolysis, the corresponding ketals can be formed (Table

2, entries 6-10). Unfortunately, *para* groups consisting of –F, –OMe, –Me and –CN could not be arylated in 24 hours. All reactions afforded α-arylated products, at 100% conversion. High yields were also achieved for the 7-membered ketal, which were only moderate in ionic liquids (also, see Chapter 2).

Table 3. Effects of different alcohols on the Heck reaction[a]



Entry	Solvent	b.p. (°C)	Conversion **4d** (%)
1		83	5
2		82	21
3		108	33
4		97	48
5		123	71
6		54	81
7		187	91
8		214	96
9		197	97

[a]Reaction conditions:**1** (3.0 equiv.), **2** (1.0 mmol), Pd $(OAc)_2$ (5.0 mol%), DPPP (10.0 mol%) and NEt_3 (2.5 equiv.) Solvent (2 mL) at 115 °C, based on 2 h time; 100% conversion and no linear products; isolated yields are reported; **4** was obtained after acidification of **3**.

An important aspect of the reaction which should be noted is the lack of byproducts produced in competing side reactions. This allows for facile separation of products from the salt and residual catalyst mixture with a simple silica plug, using DCM as an eluant. In fact, the resultant fraction from this separation technique alone produces a ^{1}H NMR of immaculate purity, and full characterisation was achieved for all compounds (also, see Section 3.6).

As alcohol solvents have seldom been exploited, it is important to understand its role in the Heck coupling reaction. A number of propanol analogues were subsequently tested, in the arylation of **1a** by **2d**. The results are presented in Table 3.

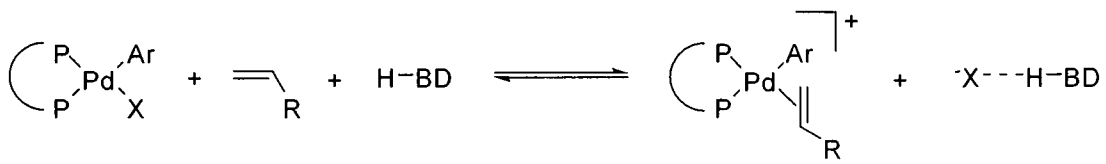
A general observation based on 2 h conversions is the superior performance of unbranched alcohols (Entries 2, 4 and 8) compared to their branched or more branched counterparts (Entries 1, 3, 5 and 7, Table 3). For example, in the case of 2-methyl isopropanol and isopropanol in entries 1 and 2, there is an obvious difference in conversion of 5% and 21%, respectively. Entries 3 and 7 deserve particular attention, as the difference of an additional –OH functionality has a profound effect on the reaction rate. Entry 6 may provide some insight into the nature of the –OH. The two $-CH_2F$ provide a strong electron withdrawing effect, and the hydrogen becomes a very good hydrogen-bond donor. Entry 8 and 9 show similar conversions, but ethylene glycol is the best solvent.

Glycerol was also used as a solvent; the reaction completed with 96% conversion. However, the mixture was found to solidify as soon as it was taken from the carousel. Given the difficulty with work up, it was omitted from the table.

An important observation is that the behaviour of the alcohol relates to H-bonding ability. The better the H-bond donor ability, the faster the arylation. Alcohols with more -OH and with easier-to-access -OH groups will yield faster rates. Diols are

stronger H-bond donors then simple alcohols, and linear alcohols are better then branched ones. Judging from the conversion and cost, even though Table 3 shows that isopropanol is a good solvent, we have found that diols and particularly ethylene glycol are a much better choice (1L ethylene glycol is £28.70, 1L 1,3-propandiol is £107.50, Aldrich).

Recently, we demonstrated that in the presence of hydrogen-bond-donating ammonium salts, such as $[HNEt_3][BF_4]$, the regioselective Heck arylation of electron-rich olefins can be performed equally well in common solvents, such as DMF.[200]



Scheme 3.04. H-BD: hydrogen-bond donor, for example, $HNEt_3^+$, HOH, HOR.

We proposed that before the rate-determining step, which is likely to be the olefin insertion step,[104,107,108,110,157,158,199,200,287] an equilibrium exists in which addition of the potential hydrogen-bond donor shifts the equilibrium to favour the cationic Pd(II)–olefin intermediate (Scheme 3.04). This leads to a higher concentration of the cationic intermediate, and hence, a higher rate for formation of the product. We also showed that this acceleration of the α-arylation by potential hydrogen-bond-donating ammonium salts is true in common solvents such as DMF, as well as in ionic liquids. However, a negative aspect arising from the application of such salts is that a large quantity of the salt is necessary, namely, 1.5 equiv relative to the substrate, which generates waste that needs to be separated and disposed of, and so has its associated environmental implications. The chemistry does, however, provide evidence that a hydrogen bond donor is at work. The current study suggests that alcohols such as

ethylene glycol can play a similar role, thus providing a more benign, more economical and simpler route to α-arylation.

When the research from this chapter was presented at an AstraZeneca conference demonstrating the outstanding performance of isopropanol as solvent for this type of Heck reaction, two papers were consequently published in the regioselective Heck internal arylation of electron rich olefins.[219,220] One paper documented the arylation of electron rich *N*-acyl-*N*-vinylamine by aryl halides,[220] but required the addition of a large amount of hydrogen-bond donating salt $[H_2NiPr_2][BF_4]$ in isopropanol (see also section 1.9.5). A new protocol for the arylation of aryl iodides, bromides and some chlorides (even though sluggish) in the highly regioselective Heck arylation of *N*-vinylacetamide was provided, avoiding the use of aryl triflates or halide scavengers. As is the problem with ammonium salts saturation is required.[220]

He and coworkers devised a simple protocol in the synthesis of functionalised heteroaryl methyl ketones in isopropanol at 85°C, in the presence of $K_3PO_4 \cdot 3H_2O$ as a base, $PdCl_2$ and $(o\text{-tolyl})_3P$, rather then a bidentante ligands, from butyl vinyl ether and a few heteroarylbromides in fair to moderate yields (also, see Chapter 1.9.5).[219]

3.3. Conclusion

The past few years has witnessed great strides in developing active and productive catalysts for the Heck reaction. These catalysts systems often do not lead to regioselective reactions in intermolecular arylation of electron rich olefins with aryl halides. Few catalytic systems have been formulated in the past two decades however, which can lead to internal arylation in a selective manner, without the use of toxic thallium or expensive silver salts, or the use of thermally labile, base sensitive and the commercially unavailable aryl triflates. In this chapter we have demonstrated a simple

and cheap protocol for the synthesis of synthetically useful aryl methyl ketones in isopropanol, from a range of olefins. Noteworthy is the arylation of **1a** and **2a** in which an excellent yield of the branched product (92%) is achieved in just 5 h which can be extended to other substrates. The limited side reactions allow facile separation for all products in Table 1 and 2. The 7-membered ketals **3fa** and **3fg** can therefore be isolated in a pure form at high yields. The reactions in isopropanol can tolerate a range of aryl group functionalities. An alternative method for the synthesis of ketals is provided, which may find uses as intermediates for anti-HIV agents or carbonyl protective groups.

Of key importance in this chapter is the role of solvent, and particularly the role of the -OH group. Notable is the enhancement in rate with diols compared to linear alcohols or branched alcohols, illustrating H-bond donating strength is of great importance in the regioselective Heck reaction. This H-bond donor capability that was first seen by the application of an ammonium salt, which required rather large equivalents of salt, and takes place in molecular solvents and ionic liquid.[200]

The limitation in the study is the difficulty the system has when coupling more stubborn substrates such as 4-bromotoluene, 1-bromo-4-fluorobenzene and 4-bromoanisole. We decided to extend our studies further in the next chapter, as the higher boiling point of ethylene glycol might allow the activation of more stubborn substrates to take part in the arylation. The role of solvent must also be explored.

3.4. Experimental Section

General

All substrates were purchased from Lancaster and Sigma-Aldrich and were used as received. A typical procedure is given for the arylation of olefins **1a**. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with an aryl halide **2** (1.0 mmol), $Pd(OAc)_2$ (11.2mg, 0.05 mmol), DPPP (42.8 mg, 0.10 mmol), and isopropanol (2 mL) under nitrogen at room temperature. Following degassing three times, **1a** (207 mg, 2.0 mmol) and NEt_3 (0.35mL, 2.5 mmol) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at the desired temperature. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. A small sample was then taken for NMR analysis. For products **4a-n** requiring acid hydrolysis, aqueous HCl (5%, 5 mL) was added and following stirring for 0.5 h, DCM (10 mL) was added. Ketals **3eb** and **3fg** were synthesised in the same manner, without acid hydrolysis. After separation of the DCM phase, the aqueous layer was washed further with DCM (2 × 10 mL), and the combined organic layer was washed with water until neutrality, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The aryl methyl ketone **4** was isolated out of the crude product via a silica gel filled Pasteur pipette using DCM as eluant. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR, MS, HRMS and elemental analysis. The following compounds ketones **4a** [93-08-3][319,320], **4b** [941-98-0] [319,320], **4c** [3900-45-6][319,320], **4d** [1009-61-6][182], **4e** [98-86-2][319,320], **4f** [445-27-2][319,320], **4g** [455-36-7][319,320], **4j** [586-37-8][319,320], **4m** [585-74-0][319,320], **4p** [127087-66-5][182,183] and ketals **3eb** [760211-67-4][251] and **3ee** [3674-77-9][288] have all been reported previously.

General procedure for the Heck arylation of vinyl ethers in isopropanol. An oven-dried, two-necked round-bottom flask containing a stirrer bar was charged with an aryl halide **2** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05mmol), DPPP (42.8 mg, 0.10 mmol), and degassed isopropanol (2 mL) under nitrogen at room temperature. Following degassing three times, vinyl ether **1** (2.0 mmol) and NEt_3 (1.5 mmol, 0.35 mL) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at 115 °C. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. A small sample was then taken for crude ^1H NMR analysis. To the rest of the mixture, aqueous HCl (5%, 5 mL) was added and following stirring for 0.5 h, DCM (10 mL) was added. After separation of the DCM phase, the aqueous layer was extracted with DCM (2 × 10 mL), and the combined organic layer was washed with water until neutrality, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The aryl methyl ketone 4 was generally isolated by a simple flash chromatography technique using silica gel plug through a pasteur pipette using DCM as an eluant. The isolated yields of the products are given in Table 1. The arylation of hydroxy alkyl ethers **1e** and **1f** involved the same procedure, the products of which can be found in Table 2 for which acid hydrolysis was omitted for entries 6-10.

General procedure for solvent effect study. The procedure for the solvent study is the same as described above for the typical arylation of vinyl ethers, however all reactions were terminated after 2 h and directly cooled to inhibit any further reaction. Acid hydrolysis was then carried out, and the procedure above was followed. The results can be found in Table 3.

3.5. Analytical Data

1-(Naphthalen-2-yl)ethanone (4a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.00-7.98 (m, 1H), 7.91-7.89 (m, 1H), 7.84-7.81 (m, 2H), 7.57-7.49 (m, 2H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 136.0, 134.8, 132.9, 130.6, 130.0, 128.9, 128.8, 128.2, 127.2, 124.3, 27.1; CI-MS *m/z* 188 [$(M + NH_4)^+$, 100], 171 (90); HRMS Calcd for $C_{12}H_{11}O$ $(M + H)^+$: 171.0810. Found: 171.0811. Anal. Calcd for $C_{12}H_{10}O$: C, 84.68, H, 5.92. Found: C, 84.76, H, 5.90.

1-(Naphthalen-1-yl)ethanone (4b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76-8.74 (d, J = 7.96 Hz, 1H), 7.90-7.87 (d, J = 8.22 Hz, 1H), 7.83-7.77 (m, 2H), 7.56-7.52 (m, 1H), 7.47-7.43 (m, 1H), 7.40-7.36 (m, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 136.0, 134.4, 133.4, 130.6, 129.0, 128.4, 126.8, 126.2, 124.7, 53.8, 30.3; CI-MS *m/z* 188 [$(M + NH_4)^+$, 88], 171 (100); HRMS Calcd for $C_{12}H_{11}O$ $(M + H)^+$: 171.0810. Found: 171.0809. Anal. Calcd for C_8H_7FO: C, 84.68, H, 5.92. Found: C, 84.50, H, 5.94.

1-(6-Methoxynaphthalen-2-yl)ethanone (4c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.89-7.88 (m, 1H), 7.86-7.85 (m, 1H), 7.62-7.60 (m, 1H) 7.09-7.01 (m, 2H) 3.81 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 160.2, 137.7, 133.1, 131.5, 130.4, 128.5, 127.5, 125.1, 120.1, 106.2, 55.8, 26.9; Cl-MS *m/z* 201 $[(M + H)^+$ 100]; HRMS Calc for $C_{13}H_{13}O_2$ $(M + H)^+$: 201.0916. Found: 201.0916. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98, H, 6.04. Found: C, 77.85, H, 6.03.

1,1'-(1,4-Phenylene)diethanone (4d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 4H), 2.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 140.5, 128.8, 27.2; CI-MS *m/z* 180 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_{10}H_{14}NO_2$ $(M + NH_4)^+$: 180.1024. Found: 180.1025. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06, H, 6.21. Found: C, 74.00, H, 6.25.

Acetophenone (4e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.58-7.53 (m, 1H), 7.48-7.43 (m, 2H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 137.6, 133.4, 128.9, 128.7, 27.0; CI-MS *m/z* 121 [$(M + H)^+$, 100], 105 (86), 83 (30); HRMS Calcd for C_8H_9O $(M + H)^+$: 121.0653. Found: 121.0656. Anal. Calcd for C_8H_8O: C, 79.97, H, 6.71. Found: C, 80.17, H, 6.68.

1-(2-Fluorophenyl)ethanone (4f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.77 (m, 1H), 7.47-7.41 (m, 1H), 7.21-7.11 (m, 1H), 7.09-7.07 (m, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2 (d, J_{CF} = 3 Hz), 162.6 (d, J_{CF} = 255 Hz), 135.0 (d, J_{CF} = 9 Hz), 131.0 (d, J_{CF} = 2 Hz), 126.1 (d, J_{CF} = 24 Hz), 124.7 (d, J_{CF} = 3 Hz), 117.0 (d, J_{CF} = 24 Hz), 31.7; CI-MS *m/z* 156 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_8H_{11}NFO$ $(M + H)^+$: 156.0825. Found: 156.0828. Anal. Calcd for C_8H_7FO: C, 69.56, H, 5.11. Found: C, 69.57, H, 5.13.

1-(3-Fluorophenyl)ethanone (4g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.71 (m, 1H), 7.65-7.61 (m, 1H), 7.48-7.41 (m, 1H), 7.29-7.23 (m, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 163.25 (d, J_{CF} = 248 Hz), 139.6 (d, J_{CF} = 6 Hz), 130.6 (d, J_{CF} = 8 Hz), 124.5 (d, J_{CF} = 3 Hz), 120.4 (d, J_{CF} = 22 Hz), 115.3, 26.9 (d, J_{CF} = 22 Hz); CI-MS *m/z* 156 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_8H_{11}NOF$ $(M + H)^+$: 156.0825. Found: 156.0827. Anal. Calcd for C_8H_7FO: C, 69.56, H, 5.11. Found: C, 69.61, H, 5.14.

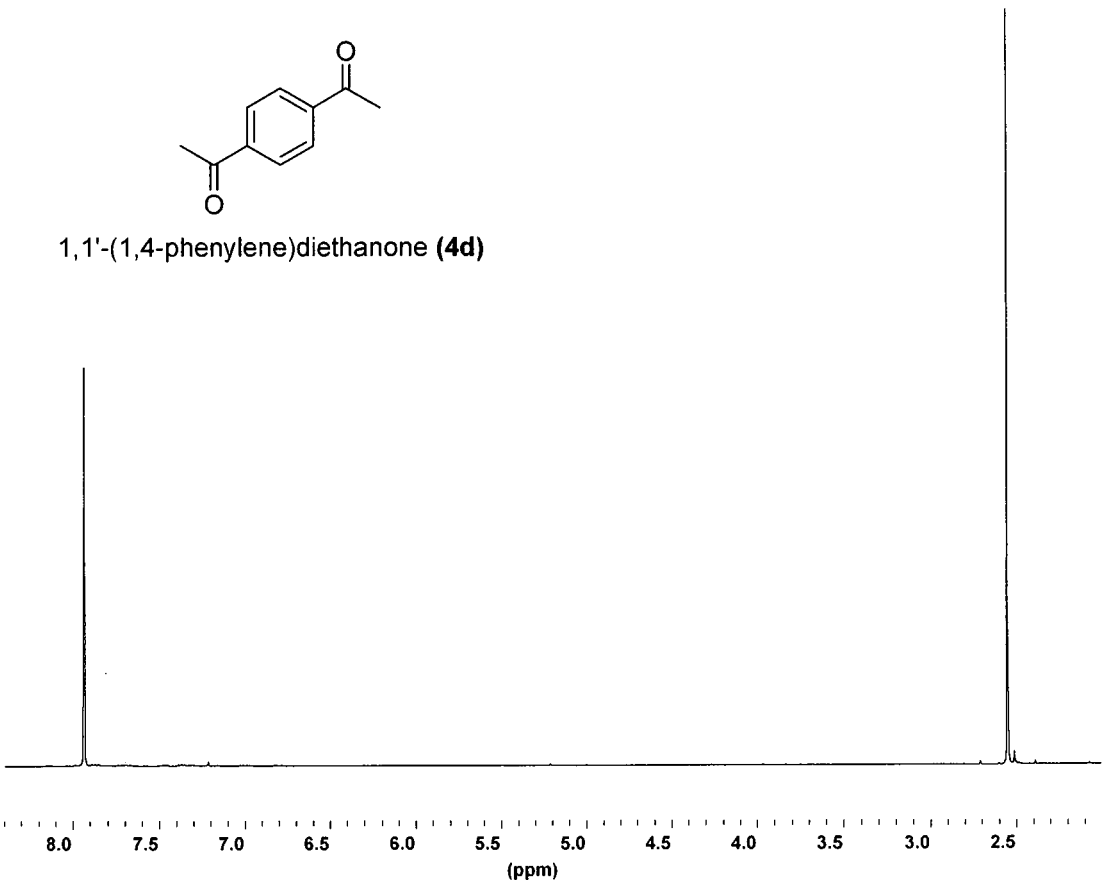
1-(3-Methoxyphenyl)ethanone (4j). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 2H), 7.36-7.30 (m, 1H), 7.10-7.06 (m, 1H), 3.81 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 160.3, 139.4, 129.9, 121.5, 120.0, 112.8, 55.8, 27.0; CI-MS *m/z* 151 [$(M + H)^+$, 32], 168 [$(M + NH_4)^+$, 100; HRMS Calcd for $C_9H_{11}O_2$ $(M + H)^+$: 151.0759. Found: 151.0759. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98, H, 6.71. Found: C, 72.19, H, 6.77.

1-*m*-Tolylethanone (4m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.71 (m, 2H), 7.35-7.28 (m, 2H), 2.58 (s, 3H), 2.41 (s, 3H); 198.7, 138.7, 137.6, 134.2, 129.2, 128.9, 126.0, 27.0, 21.7; CI-MS *m/z* 152 [$(M + NH_4)^+$, 100], 135 (32); HRMS Calcd for $C_9H_{10}O$ $(M + H)^+$: 135.0810. Found: 135.0811. Anal. Calcd for $C_9H_{10}O$: C, 80.56, H, 7.51. Found: C, 80.49, H, 7.48.

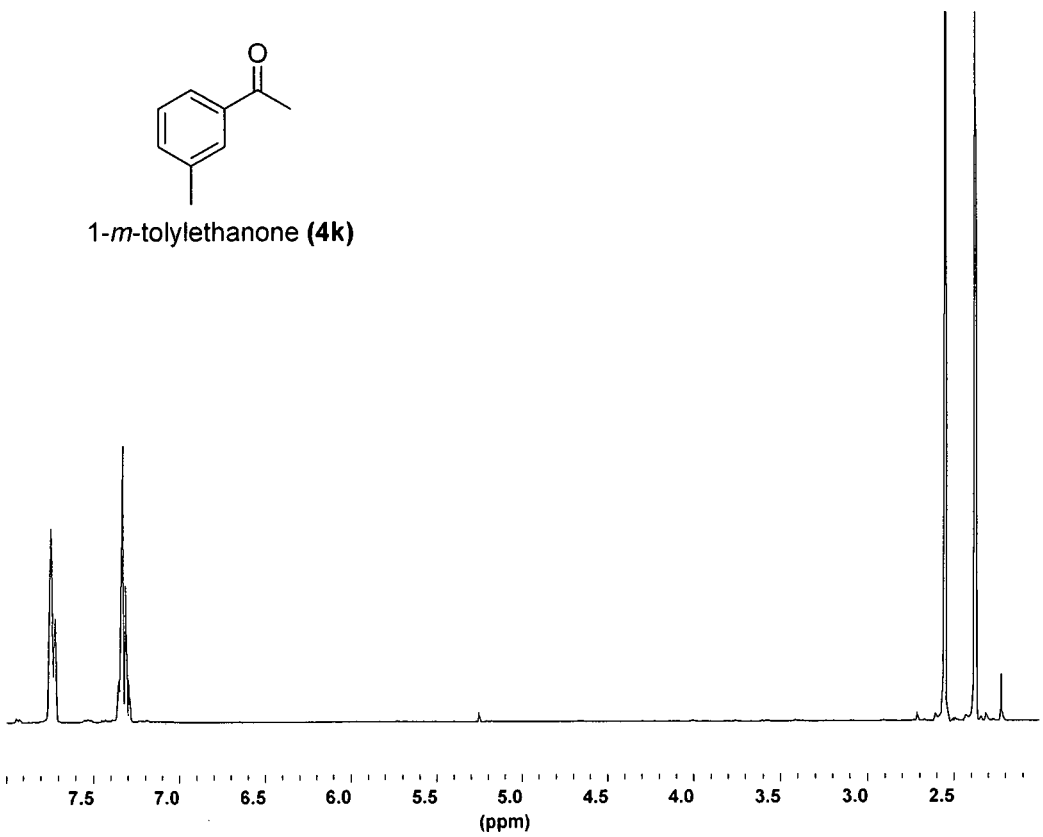
4-Acetylbenzonitrile (4p). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 6.6 Hz, 2H), 7.79 (d, J = 6.6 Hz, 2H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 142.0, 133.2, 129.2, 117.7, 115.6, 27.1; CI-MS *m/z* 163 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_{15}H_{16}NO_2$ $(M + H)^+$: 163.0871. Found: 163.0866. Anal. Calcd for C_9H_7NO: C, 74.47, H, 4.86, N, 9.65. Found: C, 74.44, H, 4.84, N, 9.58.

3.6. Sample ^{1}H NMR spectra (400 MHz, $CDCl_3$

1,1'-(1,4-phenylene)diethanone **(4d)**



1-*m*-tolylethanone **(4k)**

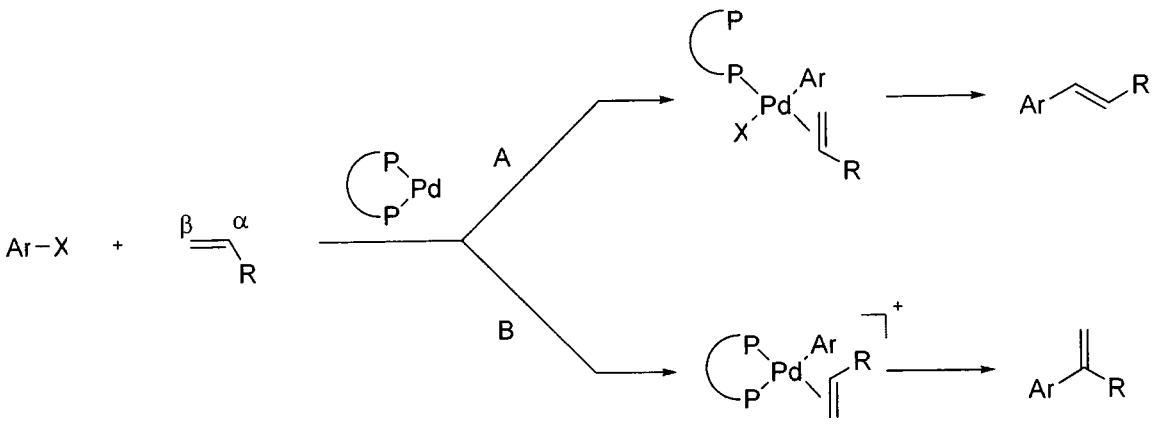


CHAPTER FOUR

A Cleaner, Faster and Regioselective Heck Arylation of Electron-Rich Olefins in Ethylene Glycol

4.1. Introduction

The formation of new sp^2 C-C bonds through the palladium-catalysed Heck reaction is one of the most important tools in synthetic chemistry.[21,34,152,175,177,291] However, a regioselectivity issue exists when electron-rich olefins are employed, which give rise to a mixture of branched α- and linear β-regioisomers, due to the operation of two reaction pathways (Scheme 4.01).[21,151,175,181,182,193,321] Extensive research by the groups of Cabri,[151,175,181,182,193] Hallberg and Larhed,[175,190-192,197,250,293] and others[187,188,294] has established two methods to deal with this problem: 1) when aryl halides are the substrates, addition of stoichiometric amounts of silver or thallium salts, and 2) use of aryl/vinyl triflates instead of the halides.[253,263,297-299,322,323] These conditions promote the ionic pathway B (Scheme 4.01) in which the branched α olefinic products are selectively produced.[157,158,240,243] However, silver introduces added cost, whereas thallium salts are toxic, and triflates are generally commercially unavailable, base sensitive, and thermally labile.



Scheme 4.01. Two possible products of the Heck reaction.

Recent DFT calculations have shed more light on the mechanisms, showing that when following the pathway A, electron-rich olefins indeed tend to afford the α-arylated olefin, and this is driven primarily by electrostatic and frontier orbital interactions.[240,243,324-326] In fact, the C-C bond forming olefin insertion step may be viewed as an intramolecular nucleophilic attack of the migrating aryl group at the olefin.[240] More recently, Amatore, Jutand and coworkers showed that isobutyl vinyl ether reacts with PdX(Ph)(DPPP) (X = I, OAc) indeed *via* a cationic species, $[Pd(Ar)(DPPP)(solvent)]^+$; but this can lead to both α– and β-products.[157,158] The kinetic study led to an altered mechanism being suggested, in which the olefin reacts with the cationic solvato-Pd(II) species generated from halide dissociation; a higher α-regioselectivity results if the subsequent equilibria involving olefin coordination and insertion are in favour of the branched product, and if the concentration of halide anion is low.[157]

Recently, we demonstrated that, in the presence of hydrogen bond-donating ammonium salts such as $[HNEt_3][BF_4]$, the regioselective Heck arylation of electron-rich olefins can be performed equally well in common solvents such as DMF.[102,104,107,108,111,199,200] We proposed that, before the rate-determining step which is likely to be the olefin insertion step,[102,104,107,108,111,157,158,199,200,287] there exists an equilibrium, in which addition of the potential hydrogen-bond donor shifts the equilibrium to favour the cationic Pd(II)-olefin intermediate (Scheme 4.02: H-BD: hydrogen-bond donor, *e.g.* $HNEt_3^+$, HOH, HOR). This leads to a higher concentration of the cationic intermediate and hence a higher rate toward the α product. We further showed that this acceleration in the α-arylation by potential hydrogen bond-donating ammonium salts is true in common solvents as well as in ionic liquids. However, a negative aspect arising from the application of such salts is that a large quantity of the

salt is necessary, *viz* 1.5 equiv. relative to the substrate, generating waste that needs to be separated and disposed of, and so has its associated environmental implications. In related work, Hallberg, Larhed and coworkers showed that regiocontrol can be effected in a DMF/water or DMF/MeOH mixture,[218] and very recently Larhed reported that water can be used as solvent for fast, highly regioselective arylation.[223] However, the chemistry of the latter appears to be restricted to hydroxyl vinyl ethers.

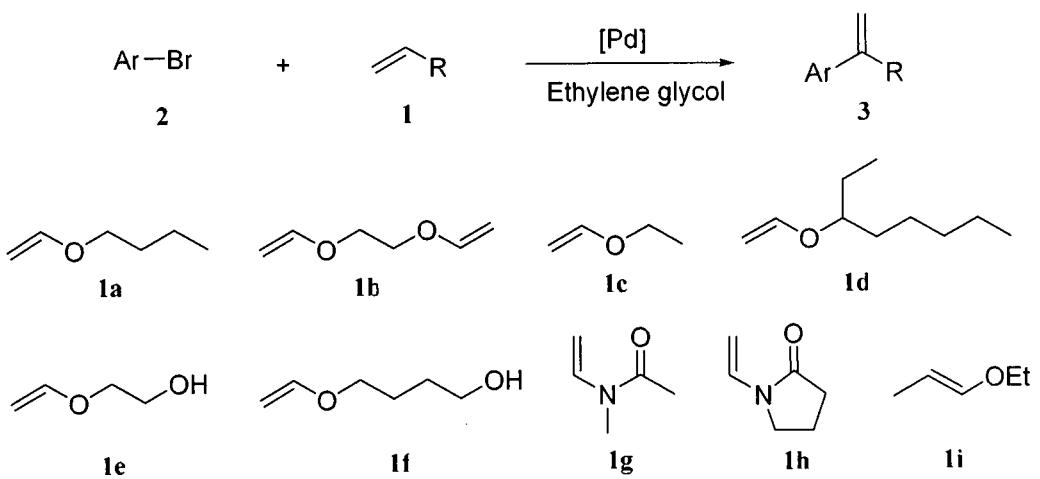
Scheme 4.02. H-BD: hydrogen-bond donor, for example, $HNEt_3^+$, HOH, HOR.

In continuing our search for a cleaner, more economic method for the regioselective Heck reaction, we reported that the Heck arylation of electron-rich olefins with aryl halides can be most easily performed *in alcohols*, specifically isopropanol, in a highly regioselective and efficient manner, requiring neither ionic liquids/ionic additives nor halide scavengers.[36,219,220,327-329] Although alcohols such as isopropanol and ethylene glycol provide remarkably economic, safe and environmentally attractive alternatives to commonly used dipolar solvents, they have been seldom exploited in metal-catalysed coupling reactions.[213,303,304,330,331] Of both practical and fundamental significance is that our further studies point to the Heck regioselectivity being directed by polar, protic solvents.

Alcohols are good hydrogen bond donors and are known to act as receptors for halide anions.[305] This feature can aid the dissociation of halide anion from Pd(II), thereby enhancing the concentration of the ionic Pd(II)-olefin species in pathway A.[197,200,223,251,307,308] Short chain alcohols are also known to have hydrogen bond

donating capabilities similar to imidazolium ionic liquids.[309-312] With this in mind, we set out to investigate whether the regioselective Heck arylation of electron-rich olefins could be affected in a simple alcohol like isopropanol, which yielded excellent selectivities (also, see Chapter 3). However, the arylation of some substrates bearing a strongly electron withdrawing group or donating group *para* to the dissociating bromide were found to be sluggish, and in some cases could not be achieved. This could be due to the operation temperature, and may require higher temperatures beyond the boiling point of isopropanol to activate.

At the end of the last chapter it was found that the reaction of **2d** with butyl vinyl ether **1a** could afford full conversion after just 2 h in diols, alongside maintaining the excellent selectivity achieved in isopropanol. 1,3-Propandiol and 1,2-ethanediol proved to yield very similar results and both have high boiling points (214 °C and 198 °C respectively). They have similar chemical properties; essentially the choice of solvent was based on cost, of which ethylene glycol is the cheapest. In this chapter, we now report the regioselective arylation of electron-rich olefins in ethylene glycol (Scheme 4.03)



Scheme 4.03. Arylation of electron-rich olefins **1a-i** in ethylene glycol.

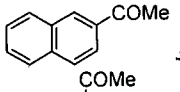
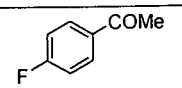
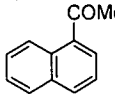
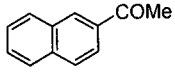
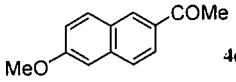
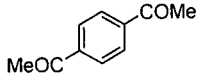
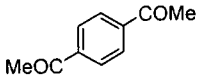
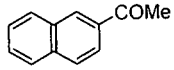
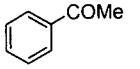
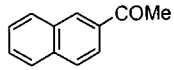
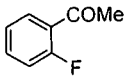
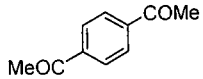
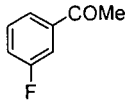
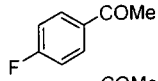
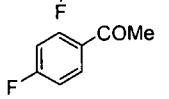
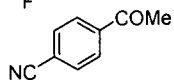
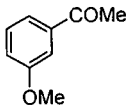
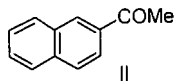
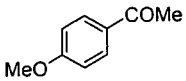
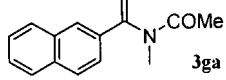
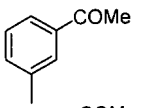
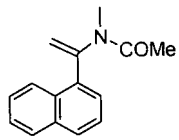
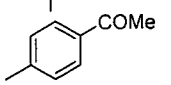
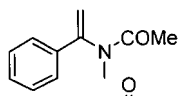
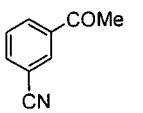
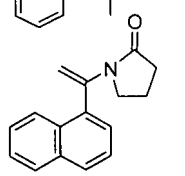
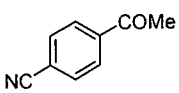
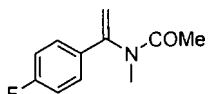
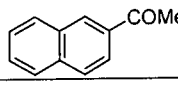
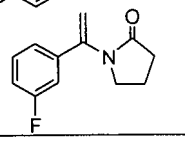
4.2. Results and Discussion

Ethylene glycol allows operation at a higher temperature then isoproanol, and may render the ionic pathway A more favourable by forming more effective hydrogen bonding with the bromide anion and thus enhancing the concentration of the cationic Pd(II)-olefin species (Scheme 4.02). The dielectric constants of isopropanol and ethylene glycol are 19.9 and 37.7, and the E_T^N values are 0.546 and 0.790, respectively; this parameter measures largely the hydrogen-bond-donating capability of a solvent (*vide infra*).[332]

As an examination of feasibility, we tested the arylation of **1a** and **2a** which underwent condtions similar to those used in isopropanol except either a higher temperature of 145 °C; delightedly we found that this benchmark reaction completed within 2 h, under Pd-DPPP catalysis with no linear product detected; the ketone **4a** was isolated after acidification of **3a** in excellent yield (Table 1, Entry 1). To probe the scope of the system, a series of vinyl ethers were tested in the arylation of a range of aryl bromides (Table 1).

Entry 1 and entry 4 had the shortest reaction time, but the reaction could not be completed in 1.5 h. Since some substrates necessitated longer times, *e.g.* the enamides, the rest of the reactions were run overnight, and in the case of the enamides up to 36 h were necessary (Entries 25-30).[321] The reactions furnished good to excellent ketone products regardless of the nature of the substituents on the aryl rings, and in no case was the linear product observed. The reaction proceeded cleanly, so that again, separation *via* a small silica plug was usually sufficient to obtain pure products. Of particular note are the *para* substituted bromides **2h**, **k** and **n**, could now be completely arylated.

Table 1. Regioselective arylation of olefins **1** in ethylene glycol[a]

Entry	Olefin	ArBr	Product		Yld (%)	Entry	Olefin	ArBr	Product		Yld (%)
1	**1a**	**2a**		**4a**	93	16	**1b**	**2h**		**4h**	78
2	**1a**	**2b**		**4b**	89	17	**1c**	**2a**		**4a**	74
3	**1a**	**2c**		**4c**	94	18	**1c**	**2d**		**4d**	76
4	**1a**	**2d**		**4d**	83	19	**1d**	**2a**		**4a**	78
5	**1a**	**2e**		**4e**	87	20	**1e**	**2a**		**4a**	88
6	**1a**	**2f**		**4f**	76	21	**1e**	**2d**		**4d**	83
7	**1a**	**2g**		**4g**	91	22	**1e**	**2h**		**4h**	87
8	**1a**	**2h**		**4h**	88	23	**1e**	**2p**		**4p**	89
9	**1a**	**2j**		**4j**	75	24	**1f**	**2f**		**4a**	93
10	**1a**	**2k**		**4k**	79	25[b]	**1g**	**2a**		**3ga**	78
11	**1a**	**2m**		**4m**	77	26[b]	**1g**	**2b**		**3gb**	79
12	**1a**	**2n**		**4n**	89	27[b]	**1g**	**2e**		**3ge**	81
13	**1a**	**2o**		**4o**	83	28[b]	**1h**	**2b**		**3hb**	74
14	**1a**	**2p**		**4p**	84	29[b]	**1g**	**2h**		**3gh**	78
15	**1b**	**2a**		**4a**	87	30[b]	**1h**	**2g**		**3hg**	82

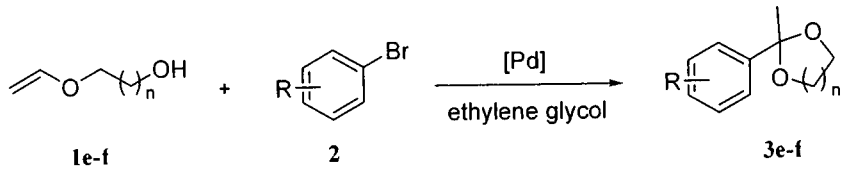
[a]Reaction conditions: 3.0 equiv. **1**, 1.0 mmol **2**, 5.0 mol% $Pd(OAc)_2$, 10.0 mol% DPPP, and 2.5 equiv NEt_3 in 2 mL ethylene glycol at 145 °C; 100% conversion and no linear products; Isolated yields; **4** was obtained after acidification of **3**. [b]Conditions were the same as for [*a*], omitting aqueous acidic work up.

Of further interest is the successful coupling of enamides **1g-h**, which have been previously arylated regioselectively in a mixture of ionic liquid and DMSO.[107] When the enamide coupling is carried out in an aprotic solvent like dioxane, aryl triflates have been the substrates instead of the halides.[188] Internal Heck vinylations of enamides have also been performed with high regioselectivity, with vinyl triflates as substrates.[190]

In the absence of an acid, the arylation product arising from 2-hydroxyethyl vinyl ether **1e** could cyclise to give synthetically useful ketals which may find uses as intermediates for anti-HIV agents and protective groups for carbonyls. This was first demonstrated by Hallberg, Larhed and coworkers using aryl triflates or halide scavengers for ArX (X = Br, I) in DMF;[191] however the reaction tends to be slow and requires further addition of dry acetic acid to complete ring closing or prolonged heating following the consumption of the arylbromide at elevated temperatures.

When **1e** was arylated in ethylene glycol under the conditions of Table 1 but without subsequent hydrolysis, the corresponding 5-memebered ketals were isolated in good yields (Table 2). Most reactions required 12 h to complete, however the reaction with **2a** required only 2 h. An example of 7-memebered ketals is also provided in entry 10, and is formed after only 2 h. After this 2 h period, it was found that a mixture of the 5- and 7-member ketal were present, leading to finally only the 5-membered ketal **3ea** after 4 h.

Table 2. Arylation of hydroxyl vinyl ether to form cyclic ketals[a]

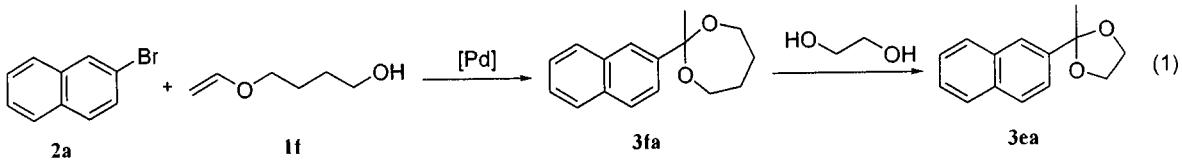


1e-f 2 3e-f

Entry	Olefin	ArBr	Product	Yld (%)	Entry	Olefin	ArBr	Product	Yld (%)
1	**1e**	**2a**	**3ea**	88	6	**1e**	**2g**	**3eg**	87
2	**1e**	**2b**	**3eb**	88	7	**1e**	**2h**	**3eh**	85
3	**1e**	**2d**	**3ed**	89	8	**1e**	**2n**	**3en**	86
4	**1e**	**2e**	**3ee**	81	9	**1e**	**2r**	**3er**	83
5	**1e**	**2f**	**3ef**	77	10	**1f**	**2a**	**3fa**	69

[a]Reaction conditions are as in Table 2, without aqueous acidic work up; 100% conversion and no linear products; Yld refers to isolated yields.

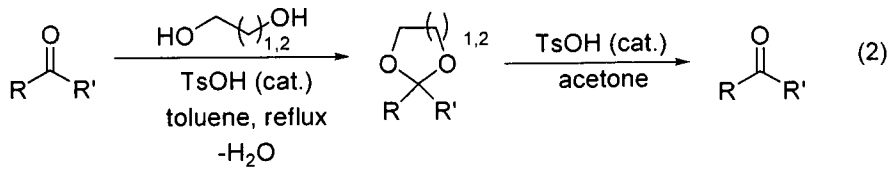
Apparently, this product arises from **3fa** reacting with the solvent to give a more thermodynamically stable product. The observation also suggests that there may be an exchange between **3ea**, **3fa** and ethylene glycol (Eq. 1).



2a 1f 3fa 3ea

1,3-Dioxanes and 1,3-dioxolanes can be typically prepared from carbonyl compounds with 1,3-propanediol or 1,2-ethanediol in the presence of a Brönsted or a Lewis acid catalyst (Eq. 2). The procedure in Eq. 2 using 1,2-diols give more stable compounds. A standard procedure for protection employs toluenesulfonic acid as

catalyst refluxing in toluene, which allows the continuous removal of water from the reaction mixture using Dean-Stark apparatus.[333] A mixture of orthoesters or molecular sieves can also provide effective water removal through chemical reaction or physical sequestration. Our method allows ketals to be prepared from aryl halides.



(2)

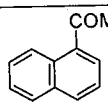
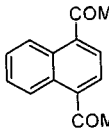
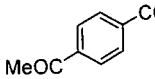
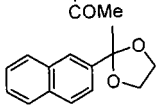
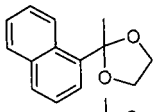
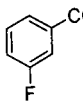
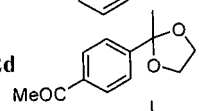
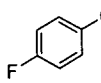
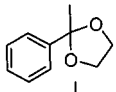
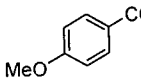
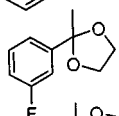
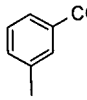
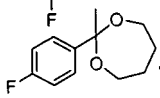
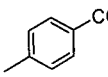
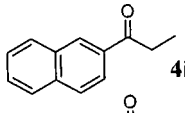
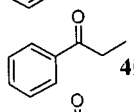
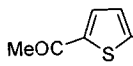
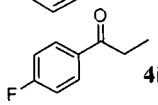
We have previously shown that ketals are formed in similar reactions in ionic liquids[107,199] (Chapter 2), and also isopropanol (Chapter 3), and in both these solvents and ethylene glycol excellent α-regioselectivities were maintained. As aforementioned, hydroxyl vinyl ethers also gave an excellent regioselectivity when using water as solvent. Larhed and coworkers have further shown that the reaction works to some degree even in toluene.[223] The hydroxyl group thus appears to play a role similar to that of an alcohol solvent (*vide infra*). Larhed shows that the hydroxyl vinyl ether **1e** reacts with aryl bromides regioselectively in toluene and suggests this may be due to the dissociation of a bromide from Ar-Pd-Br being facilitated by –OH which hydrogen bonding to the Br^-.[223] It is remarkable that when carried out in DMF using a tetradentate phosphine, the reaction of **1e** favoured the β product.[334] Interestingly, Kondolff and coworkers utilised a Tedicyp/palladium-catalysed system in DMF in the coupling of hydroxyl ethyl vinyl ether with 4-bromoacetophenone, producing 93% of the linear ketal product, and 7% of the branched ketal. The same reaction in ethylene glycol gave no product.[251]

In the reactions in ethylene glycol described above, the arylation procedure involved heating a mixture of all the reagents together. It was noted that the ethylene glycol solution turned dark almost immediately, indicating the formation of palladium black.[335]

After a series of test reactions, it became apparent that the presence of the olefin from the beginning was enhancing the rate of Pd(II) reduction to palladium black before forming the Pd-DPPP catalyst. In line with this, when the olefin substrate was added 3-4 min after the solution had been heated, the initial yellow orange solution only turned dark brown slowly, suggesting the presence of more Pd-DPPP complex in the catalyst.

In a separate experiment, it was observed that in the presence of **1a**, an isopropanol solution of $Pd(OAc)_2$ turned dark in less than 1 min at room temperature; in its absence the solution remained yellow for more than 20 h, indicating again that Pd(II) is easily reduced by the olefin. This simple change in procedure was implemented to the arylation and we were delighted to find that the reaction in ethylene glycol proceeds at a much faster rate, even at lower catalyst loadings. Selected examples are illustrated in Table 3, including the coupling of a 2-substituted olefin **1i**. For all the substrates, particularly the previously "stubborn" **2h**, **2k** and **2n**, the reaction time reduced dramatically compared to those presented in Tables 1 and 2, at a lower catalyst loading of 1%. Noteworthy is also the successful arylation of aryl di-bromides **2w** and **2y** (Entries 10 and 11), requiring only short times for complete conversions. The 7-membered ketal of 4-fluorobenzene **2h** could also be synthesised. However if the reaction time was longer than 0.5 h, the 5-membered analogue would be obtained (Eq. 1). This was true for many of the couplings reactions with vinyl ether **1f**. To the best of our knowledge, these examples represent the fastest rates ever reported for the Heck reaction of electron-rich olefins.

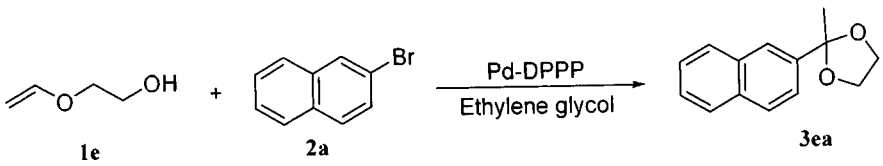
Table 3. Faster, regioselective arylation in ethylene glycol[a]

Entry	Olefin	ArBr	Product	Time (h)	Yld (%)	Entry	Olefin	ArBr	Product	Time (h)	Yld (%)
1	**1a**	**2b**	 **4b**	0.5	77	11[b]	**1a**	**2y**	 **4y**	1	82
2	**1a**	**2d**	 **4d**	0.5	83	12[c]	**1e**	**2a**	 **3ea**	0.5	76
3	**1a**	**2e**	 **4e**	0.5	85	13[c]	**1e**	**2b**	 **3eb**	2	88
4	**1a**	**2g**	 **4g**	1	91	14[c]	**1e**	**2d**	 **3ed**	0.5	76
5	**1a**	**2h**	 **4h**	1	89	15[c]	**1e**	**2e**	 **3ee**	0.5	73
6	**1a**	**2k**	 **4k**	2	84	16[c]	**1e**	**2g**	 **3eg**	0.5	73
7	**1a**	**2m**	 **4m**	0.5	78	17[c]	**1f**	**2h**	 **3fh**	0.5	71
8	**1a**	**2n**	 **4n**	2	71	18	**1i**	**2a**	 **4ia**	3	72
9	**1a**	**2t**	 **4t**	0.5	81	19	**1i**	**2e**	 **4ie**	3	75
10[b]	**1a**	**2w**	 **4w**	1.5	69	20	**1i**	**2h**	 **4ih**	3	81

[a]Reaction conditions: 3.0 equiv. **1**, 1.0 mmol **2**, 1.0 mol% $Pd(OAc)_2$, 2.0 mol% DPPP, and 2.5 equiv. NEt_3 in 2 mL ethylene glycol at 145 °C, with **1** added 3-4 minutes after the mixture containing all the other reagents had been heated at 145 °C; 100% conversion and no linear products detected; isolated yields; **4** was obtained after acidification of **3**. [b]Conditions were the same as for [*a*]; however **2w** and **2y** are dibromides and 6.0 equiv **1** were used. [c]Conditions were the same as for [*a*], omitting aqueous acidic work up.

An additional advantage of the protocol is that it allows both the Pd-DPPP catalyst and solvent to be easily recycled, since the product could be extracted with a less polar solvent. To demonstrate this, the regioselective arylation of **1e** with **2a** was examined in ethylene glycol. Following each run, the ketal was extracted with diethyl ether. As can

be seen from Eq. 3, the Pd/DPPP-ethylene glycol mixture was recycled 5 times with no significant loss in catalytic activity.

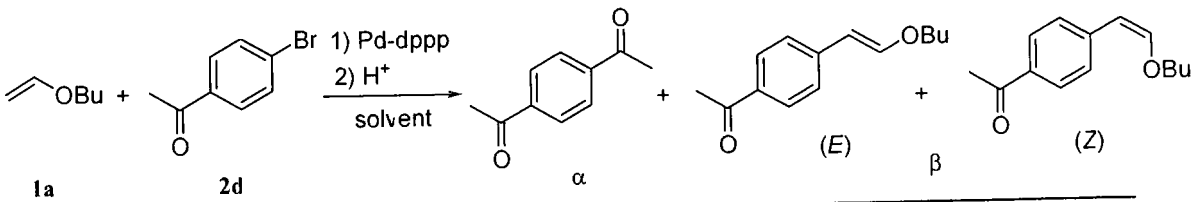


1e 2a 3ea (3)

Run	1	2	3	4	5
Isolated Yields (%)	91	87	84	82	86

The study into the regioselectivity of the Heck reaction has attracted a great deal of attention in the past two decades or so, culminating with the advent of three effective methods to control the α-regioselectivity (*vide supra*). It is all surprising that a simple switch of solvents from the common dipolar solvents like DMF or ionic liquids to an alcohol affords complete regiocontrol for electron-rich olefins, with no need for any halide scavengers. Naturally, one would like to ask why the alcohol solvents are so effective in promoting the α-regioselectivity. We started this study by assuming that alcohols could act as hydrogen bond donors, stabilising or solvating the dissociated halide anions and thereby enhancing the concentration of the key cationic Pd-olefin intermediate (pathway B, Scheme 4.02). If this is true, other protic solvents would function in a similar manner. In particular, solvents with high E_T^N values would be expected to furnish good α-regiocontrol, as they are in general good hydrogen-bond donors (*vide supra*). To quite a degree, the previous reports from Hallberg, Larhed and us on using a water-DMF mixture,[218] neat water,[223] and ammonium salts (e.g. $HNEt_3^+$)[200] to direct regioselection appear to support this view, as all these media possess hydrogen bond donating capabilities.

Table 4. Solvent effect on the Heck arylation of **1a** by **2d**[a]



1a **2d**

Solvent	b.p. [°C]	ε_r	μ [10^{-30} Cm]	E_T^N	Conversion[b] [%]	α/β[c]	*E*/*Z*	TOF$^{\alpha}$[d] [h^{-1}]
1,2-Dimethoxyethane	84.5	7.2	5.7	0.231	7.4	18:82	79:21	0.4
Triethylene glycol dimethyl ether	216	7.6	7.4	0.253	4.4	69:31	80:20	1.0
Hexamethylphosphoric triamide	233	29.3	18.5	0.315	60	11:89	74:26	2.1
N,N-Dimethylformamide	153.1	36.71	12.7	0.386	34	22:78	77:23	2.5
2-Methyl-2-propanol	82.3	12.47	5.5	0.389	4.0	>99:1	/	1.4
N,N-Dimethylacetamide	166.1	37.78	12.4	0.401	42	19:81	76:24	2.6
Dimethyl sulfoxide	189	46.45	13.5	0.444	23	44:56	73:27	3.3
3-Pentanol	115.3	13.35	5.5	0.463	9.0	>99:1	/	3.0
2-Pentanol	119	13.71	5.5	0.488	7.5	>99:1	/	2.5
2-Butanol	99.5	16.56	5.5	0.506	10	>99:1	/	3.3
2-Propanol	82.2	19.92	5.5	0.546	13	>99:1	/	4.3
2-Methyl-1-propanol	107.9	17.93	6.0	0.552	14	>99:1	/	4.7
1-Pentanol	138	13.9	5.7	0.568	16	>99:1	/	5.3
1-Butanol	117.7	17.51	5.8	0.586	22	>99:1	/	7.3
1-Propanol	97.2	20.45	5.5	0.617	30	>99:1	/	10
Ethanol	78.3	24.55	5.5	0.654	28	>99:1	/	9.4
N-Methylacetamide	206.7	191.3	12.8	0.657	49	60:40	75:25	9.7
Triethylene glycol	288	23.69	10.0	0.682	7.5[e]	>99:1	/	15
Diethylene glycol	245.7	31.69	7.7	0.713	21[e]	>99:1	/	42
N-Methylformamide	200	182.4	12.9	0.722	31[e]	>99:1	/	62
Ethylene glycol	197.5	37.7	7.7	0.790	28[e]	>99:1	/	56

[a]Reaction conditions: 3.0 equiv. **1a**, 1.0 mmol **2d**, 1.0 mol% $Pd(OAc)_2$, 2.0 mol% DPPP, and 2.5 equiv. NEt_3 in 2 mL solvent at 115 °C for 3 h; average of two runs; solvent parameters from reference 311. [b]Determined by ^1H NMR. [c]When the β product was not detected by ^1H NMR, a >99/1 ratio was assigned. [d]TOF$^{\alpha}$ refers to turnover frequency for the α product calculated using the conversions. [e]30 min reaction time.

To gain more evidence and building on the results reported in Chapter 3, we then screened a diverse range of solvents. Our study of the arylation of **1a** with **2d** in 21 solvents is summarised in Table 4.

Depending on the results used, the reaction of **1a** with **2d** can produce a mixture of α- and β-regioisomers and the latter, if formed, is usually composed of *E* and *Z* stereoisomers. In the table, the conversion refers to the total conversion of **2d** into the α- and β-olefins, while TOF^{α} denotes turnover frequency to the α product.

The solvents examined span a wide range of the solvent spectrum, as reflected in their dielectric constants ε_r (7.2-191.3), dipole moments μ (5.5×10^{-30} - 12.9×10^{-30} Cm), and E_T^N values (0.23 – 0.79). Looking through the table, there appears to be no correlation between ε_r or μ with either the conversion or TOF^{α}. However, whilst the E_T^N values do not show a correlation with the conversion, there appears to be a link between this parameter and TOF^{α}. In fact, plotting $\ln TOF^{\alpha}$ against the E_T^N reveals a rough linear relationship – the higher the E_T^N values, the faster the α-product is formed (Figure 4.01).

Since the E_T^N parameter measures largely the hydrogen bond donating capability of a solvent, this rough correlation suggests that the ionic pathway B (Scheme 4.01) and hence the formation of the α-product are accelerated by hydrogen bond donors, echoing our aforementioned proposition.

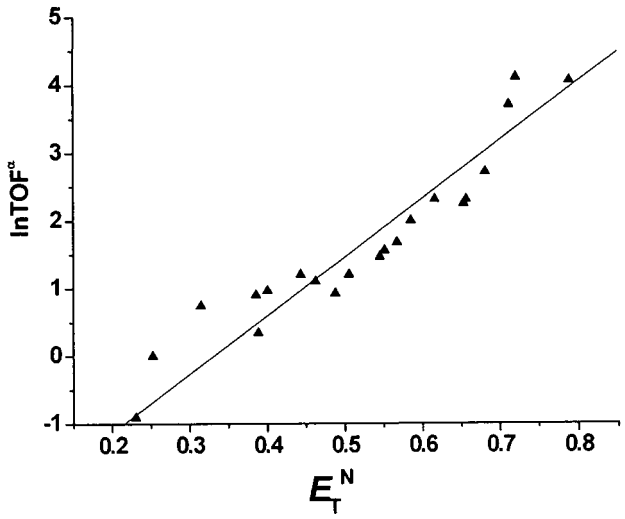


Figure 4.01. Effect of the solvent parameter E_T^N on TOF$^{\alpha}$ in the arylation of 4-bromoacetophenone with butyl vinyl ether (data taken from Table 4).

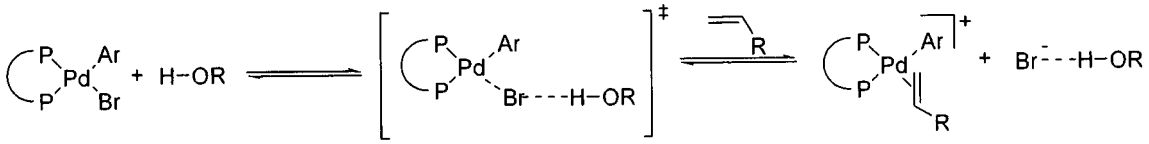
A closer look at the Table 5 shows that the α-product is exclusively produced in all the protic solvents except for *N*-methylacetamide. The alcohols deserve particular attention: in none of these solvents was the β-product ever detected, and a clear correlation between the hydrogen bond donating capabilities and the TOF$^{\alpha}$ exists; all the terminal alcohols afforded higher TOF$^{\alpha}$ than their internal isomers, with the best hydrogen bond donor ethylene glycol standing out as the best solvent. In sharp contrast, when performed in largely non-protic poly(ethylene glycol) (MW 2000) using $Pd(OAc)_2$ without ligand, the coupling of **1a** with **2** yields exclusively the α-product.[336,337]

In the recent studies of Amatore, Jutand and coworkers,[157,158] the high α-regioselectivity observed in ionic liquids[102,104,107,108,111,200] was attributed to the high ionic strength of the solvent, which encourages anion-cation separation and so enhances the concentration of the Pd(II)-olefin cations and consequently the selectivity towards

the α product. In both our previous and the current investigations, increasing the ionic strength is found to indeed increase the arylation rates.[200] Within the limited range of variation in ionic strength we examined, however, the ionic strength does not appear to have an impact on the regioselectivity. For instance, we introduced 0.5 equiv. of $[NEt_4][BF_4]$ (relative to the arylbromide) to the arylation of **1a** with **2d** in DMF which resulted in an increase in TOF by 1.5 times. Whilst this is consistent with the kinetic study of Amatore and Jutand, which showed that PdI(Ph)(DPPP) reacts faster with an analogue of **1a** at higher ionic strength,[157] the α/β ratio of the product from **1a** and **2d** remained at *ca* 22:78. A similar observation was made with $NaPF_6$. The effect of higher equivalents of salt was also investigated. However, the reduced solubility of the salt in the solvent obscured the results obtained. On the other hand, we note that the ionic strength of an ionic liquid, such as $[bmim][BF_4]$, is significantly higher then that of the solution we examined, assuming ionic strength can be calculated with $I = 0.5\Sigma_i^2 C_i$, in which Z_i is the charge of ion i and C_i is the concentration of the ion, and provided the salt is fully ionised in the solvent.

It thus appears that it is the hydrogen bond donating capabilities, not ionic strength, that make simple alcohols such powerful solvents in accelerating the α-regioselective Heck arylation. In fact, it has long been known that such solvents "exert an electrophilic pull on the departing anions in much the same way that heavy metal ions (Ag^+, Hg^{2+}) catalyse nucleophilic substitution reactions of haloalkanes", explaining why no halide scavengers are necessary in alcohols. By analogy with the S_N1 nucleophilic substitution of haloalkanes, not only may the alcohols solvate the ionised bromide anion, they could also aid its departure from Pd(II) as illustrated in Scheme 4.04. The standard molar Gibbs energies of transfer of single bromide anions from water is ΔG = 7 kJ mol^{-1} to ethylene glycol, 18.2 kJ mol^{-1} to EtOH, 22.0 kJ mol^{-1} to *i*PrOH, 27.4 kJ mol^{-1} to DMSO,

36.2 kJ mol^{-1} to DMF, 44.0 kJ mol^{-1} to DMA and 46.0 kJ mol^{-1} to HMPA.[338] This provides an estimate on how well the Br^- ions are solvated by the alcohols in comparison with the dipolar, aprotic solvents commonly used in the Heck reaction.



Scheme 4.04. Alcohols helping the departure of bromide anion.

To add further evidence, we compared the benchmark reaction using hydroxyl ethyl vinyl ether and **2a** reaction in ethylene glycol and 1,2-dimethoxyethane using the improved pre-mixing procedure. In ethylene glycol, the conversion to the Heck product was ca 80% in 20 mins; in the latter, which is no longer a hydrogen bond donor, no conversion was observed under otherwise the same conditions and 1 hr later!

4.3. Conclusion

This report presents the first general, "green" method for the Heck arylation of electron-rich olefins. Our results show that highly efficient and regioselective arylation of a number of electron-rich olefins with a range of aryl bromides which can be readily carried out in simple alcohols, circumventing the need for silver, thallium, or ammonium salts including ionic liquids. Interestingly, the arylation was successful at low catalyst loadings of 1 mol% Pd. The facile arylation of not only heterocycle thiophenes (**2t**), but also dibromides **4w** and **4y** were completed within 0.5-1 h. A robust system is demonstrated here, representing rates in the arylation of electron-rich olefins which have never been seen before at these loadings. Of further interest is the arylation to substituted olefins, which can also be arylated in fast times of only 3 h at 1 mol% Pd

loading. The chemistry is more general, greener, and less expensive than the methods reported thus far.

We believe that the excellent performance of the catalytic system stems from the solvents being dipolar, and more importantly, being hydrogen bond donors. This belief is further strengthened by the study of a benchmark electron-rich olefin reacting with an arylbromide in 21 solvents, which revealed that hydrogen-bond donating, protic solvents accelerate α-regioselective arylation. The higher the E_T^N values, the faster this reaction becomes. Whilst the detailed acceleration mechanism is yet to be scrutinised, we may conclude that dipolar, hydrogen bond donor solvents like alcohols promote the α arylation by *facilitating* bromide dissociation from Ar-Pd(II)-Br and *suppressing* its recombination with the resulting cationic Ar-Pd(II) species by –OH hydrogen-bonding with (or solvating) the Br^-. We note this proposition is not necessarily in conflict with the mechanism suggested by Amatore, Jutand and coworkers.[157] It is possible that by quenching the halides by hydrogen bonding with the solvent, the pathway in their mechanism leading to the β-product is blocked, thereby rendering the α-product favourable.

More than three decades ago, Gutmann recommended that reactive cations are best produced in solvents of high acceptor numbers.[339,340] These solvents are generally good hydrogen bond donors, *e.g.* water and short chain alcohols. This recommendation appears still fitting for the Heck reaction of electron-rich olefins.

4.4. Experimental Section

General

All reactions were carried out under a nitrogen atmosphere. The olefins **1**, aryl halides **2**, $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (DPPP), triethylamine, and all solvents were purchased from Lancaster and Aldrich and were used as received. Chromatographic purifications were performed through a silica gel (mesh 230-400) plug for the ketals **3** and ketones **4**, and by the flash technique for the enamides **3**. ^1H and ^{13}C NMR spectra were recorded on a Gemini 400 spectrometer at 400 (^1H) and 100 MHz (^{13}C) in ppm with reference to TMS internal standard in $CDCl_3$. Mass spectra were obtained by chemical ionisation (CI). The products were satisfactorily characterised by ^1H and ^{13}C NMR, MS, HRMS and in some cases elemental analysis. When possible, comparison of NMR spectra has been made with available literature data including our previous data. [105,107,199,200] The following compounds ketones **4a** [93-08-3][319,320], **4b** [941-98-0] [319,320], **4c** [3900-45-6][319,320], **4d** [1009-61-6][182], **4e** [98-86-2][319,320], **4f** [445-27-2][319,320], **4g** [455-36-7][319,320], **4h** [403-42-9][319,320], **4j** [586-37-8][319,320], **4k** [100-06-1][319,320], **4m** [585-74-0][319,320], **4n** [122-00-9][319,320], **4o** [6136-68-1] [319,320], **4p** [127087-66-5][182,183], **4t** [88-15-3][341], **4w** [4927-10-0][342], ketals **3ea** [69470-12-8][200], **3eb** [760211-67-4][251], **3ed** [105752-35-0][192], **3ee** [3674-77-9][288] and compounds **4ia** [6315-96-4][343], **4ih** [456-03-1][344], **4ie** [93-55-0][345] and enamides **3ga** [839721-26-5][107], **3gb** [141171-88-2][182] and **3gh** [839721-24-3][200] have all been reported previously.

General procedure for the Heck arylation of vinyl ethers and enamides in ethylene glycol. An oven-dried, two-necked round-bottom flask containing a stirrer bar was charged with an aryl bromide **2** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol, 11 mg), DPPP (0.10 mmol, 41 mg), and ethylene glycol (2 mL) under nitrogen at room temperature.

Following degassing three times, vinyl ether **1** (3.0 mmol) and NEt_3 (2.5 mmol, 0.35 mL) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at 145 °C. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. A small sample of **3** was then taken for NMR analysis. To the rest of the mixture, aqueous HCl (5%, 5 mL) was added yielding **4** and following stirring for 0.5 h, DCM (10 mL) was added. For the enamides, no HCl was added, however. The rest of the mixture was extracted with DCM (2 × 10 mL), and the combined organic layer was washed with water until neutrality, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The aryl methyl ketone **4** was isolated out of the crude product by a simple flash chromatography technique using silica gel plug through a pasteur pipette using DCM as an eluant. The isolated yields of the products are given in Table 1 of the text. The aryl enamide product was isolated from the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1/99 to 10/90) as eluant, the yields of which are given in Table 1.

General procedure for the Heck arylation of hydroxyl vinyl ethers in ethylene glycol. An oven-dried, two-necked round-bottom flask containing a stirrer bar was charged with an aryl bromide **2** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol, 11 mg), DPPP (0.10 mmol, 41 mg), and ethylene glycol (2 mL) under nitrogen at room temperature. Following degassing three times, a hydroxyl ethyl vinyl ether **1e** or **1f** (3.0 mmol) and NEt_3 (2.5 mmol, 0.35 mL) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at 145 °C. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. A small sample was then taken for NMR analysis. No addition of HCl was necessary. The mixture was extracted with DCM (2 × 10 mL), and the combined organic layer was washed with water until neutrality, dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

Isolated products were extracted using a silica plug, yields of which are given in Table 2.

General procedure for the recycle of the Heck arylation in ethylene glycol. The above procedure was used for the aryaltion of **1e**. After cooling down, the reaction mixture was washed with diethyl ether (5 x 10 mL) and the combined organic layer was washed with water, dried, filtered and reduced. The sample was separated from any Pd *via* a silica plug and analysed. The catalyst and ethylene glycol mixture was briefly vacuumed to remove residual diethyl ether, and the vessel was then recharged with substrates and base for the next run.

The altered procedure (Table 3) was the same as the above, except that the catalyst loading was lowered and **1a** was introduced 3-4 minutes after the mixture containing all the other reagents had been heated at 145 °C. The reaction time was significantly shorter with the new procedure (Table 3). The solvent effect was studied using the new procedure. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR, MS, HRMS and elemental analysis.

4.5. Analytical data

1-(4-Fluorophenyl)ethanone (4h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.96 (m, 2H), 7.16-7.10 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 166.1 (d, J_{CF} = 250 Hz), 134.0 (d, J_{CF} = 3.0 Hz), 131.3 (d, J_{CF} = 9.0 Hz), 116.0 (d, J_{CF} = 22 Hz), 26.8; CI-MS *m/z* 156 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_8H_{11}FNO$ $(M + NH_4)^+$: 156.0825. Found: 156.0829. Anal. Calcd for C_8H_7FO: C, 69.56, H, 5.11. Found: C, 69.15, H, 4.94.

1-(4-Methoxyphenyl)ethanone (4k). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 3.71 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 163.8, 130.9, 130.8, 114.0, 55.7, 26.5; CI-MS *m/z* 168 [$(M + NH_4)^+$, 36], 151 [$(M + H)^+$, 100]; HRMS Calcd for $C_9H_{11}O_2$ $(M + H)^+$: 151.0759. Found: 151.0759. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98, H, 6.71. Found: C, 72.10, H, 6.74.

1-*p*-Tolylethanone (4n). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 2.55 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 144.2, 135.2, 129.6, 128.8, 26.8, 21.9; CI-MS *m/z* 152 [$(M + NH_4)^+$, 100], 135 (76); HRMS Calcd for $C_9H_{11}O$ $(M + H)^+$: 135.0810. Found: 135.0809. Anal. Calcd for $C_9H_{10}O$: C, 80.56, H, 7.51. Found: C, 80.33, H, 7.54.

3-Acetylbenzonitrile (4o). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.18 (m, 2H), 7.88-7.84 (m, 1H), 7.68-7.62 (m, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 138.1, 136.4, 132.7, 132.4, 130.1, 118.4, 113.4, 27.0; CI-MS *m/z* 163 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_9H_{11}N_2O$ $(M + NH_4)^+$: 163.0871. Found: 163.0867. Anal. Calcd for C_9H_7NO: C, 74.47, H, 4.86, N, 9.65. Found: C, 74.18, H, 4.88, N, 9.39.

***N*-Methyl-*N*-(1-(naphthalen-2-yl)vinyl)acetamide (3ga).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.68 (m, 4H), 7.48-7.38 (m, 3H), 5.72 (s, 1H), 5.22 (s, 1H), 3.07 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 149.5, 134.0, 133.7, 133.1, 129.6, 128.9,

128.0, 127.1, 126.0, 125.3, 123.9, 113.2, 36.1, 22.2; CI-MS *m/z* 226 [$(M + H)^+$, 100]; HRMS Calcd for $C_{15}H_{16}NO$ $(M + H)^+$: 226.1232. Found: 226.1227.

***N*-Methyl-*N*-(1-(naphthalen-1-yl)vinyl)acetamide (3gb).** ^1H NMR (400 MHz, $CDCl_3$) δ 8.18-8.14 (m, 1H), 7.82-7.64 (m, 2H), 7.50-7.28 (m, 4H), 5.39 (s, 1H), 5.14 (s, 1H), 3.01 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 148.2, 133.7, 133.2, 129.4, 129.1, 128.0, 127.1, 126.9, 125.6, 123.9, 124.0, 113.6, 35.3, 24.2; CI-MS *m/z* 226 [$(M + H)^+$, 100]; HRMS Calcd for $C_{15}H_{16}NO$ $(M + H)^+$: 226.1232. Found: 226.1233.

***N*-Methyl-*N*-(1-phenylvinyl)acetamide (3ge).** ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 5H), 5.58 (s, 1H), 5.11 (s, 1H), 2.98 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 149.4, 135.9, 129.3, 125.9, 112.6, 53.9, 35.7, 22.0; CI-MS *m/z* 176 [$(M + H)^+$, 100]; HRMS Calcd for $C_{11}H_{14}NO$ $(M + H)^+$: 176.1075. Found: 176.1074.

1-(1-(Naphthalen-1-yl)vinyl)pyrrolidin-2-one (3hb). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.88 (m, 1H), 7.83-7.79 (m, 2H), 7.48-7.38 (m, 4H), 5.80 (s, 1H), 5.11 (s, 1H), 3.18 (t, J = 7.0 Hz, 2H), 2.48 (t, J = 8.0 Hz, 2H), 1.85-1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 142.3, 135.9, 133.7, 131.7, 129.3, 128.8, 127.5, 127.1, 126.8, 125.7, 125.1, 108.5, 48.9, 32.8, 18.4; CI-MS *m/z* 238 [$(M + H)^+$, 100]; HRMS Calcd for $C_{16}H_{16}NO$ $(M + H)^+$: 238.1232. Found: 238.1231.

***N*-(1-(4-Fluorophenyl)vinyl)-*N*-methylacetamide (3gh).** ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 7.10-7.05 (m, 2H), 5.62 (s, 1H), 5.21 (s, 1H), 3.08 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 163.7 (d, J_{CF} = 249 Hz), 148.6, 127.9 (d, J_{CF} = 8.0 Hz), 124.0, 116.4 (d, J_{CF} = 24 Hz), 112.4, 35.8, 22.1; CI-MS *m/z* 194 [$(M + H)^+$, 100]; HRMS Calcd for $C_{11}H_{13}FNO$ $(M + H)^+$: 194.0981. Found: 194.0976.

1-(1-(3-Fluorophenyl)vinyl)pyrrolidin-2-one (3hg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 7.18-6.98 (m, 2H), 5.39 (s, 1H), 5.24 (s, 1H), 3.63-3.46 (m, 2H), 2.58-2.43 (m, 2H), 2.17-2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 163.2 (d, J_{CF} = 245 Hz), 143.2, 139.1 (d, J_{CF} = 8.0 Hz), 130.3 (d, J_{CF} = 8.0 Hz), 128.7, 122.4, 115.6 (d, J_{CF} = 21 Hz), 109.4, 49.9, 32.2, 18.9; Cl-MS *m/z* 206 [$(M + H)^+$, 100]; HRMS Calc for $C_{12}H_{13}FNO$ $(M + H)^+$: 206.0981. Found: 206.0985.

2-(4-Perfluorohexylphenyl)-2-methyl-1,3-dioxolane (3er). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.59 (m, 4H), 4.08-4.02 (m, 2H), 3.80-3.71 (m, 2H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 133.1(t, J_{CF} = 24 Hz), 132.6, 126.5 (t, J_{CF} = 7 Hz), 108.6, 65.0, 27.8. The carbons in the perfluorocarbon chain were not observed.

1-(Thiophen-2-yl)ethanone (4t). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.70 (m, 1H), 7.65-7.63 (m, 1H), 7.14-7.12 (m, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 145.0, 134.2, 132.9, 128.5, 27.3; Cl-MS *m/z* 144 [$(M + NH_4)^+$, 100], 124 (39); HRMS Calcd for C_6H_7SO $(M + H)^+$: 127.0218. Found: 127.0221. Anal. Calcd for C_6H_6OS: C, 57.11, H, 4.79. Found: C, 57.35, H, 4.84.

1,1'-(Thiophene-2,5-diyl)diethanone (4w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 2H), 2.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 150.1, 132.2, 27.3; Cl-MS *m/z* 221, [$(M + NH_4)^+$, 100], 111 (34); HRMS Calcd for $C_8H_{12}SO_2N$ $(M + NH_4)^+$:186.0589. Found: 186.0592. Anal. Calcd for $C_8H_8O_2S$: C, 57.12, H, 4.79. Found: C, 56.88, H, 4.82.

1,1'-(Naphthalene-1,4-diyl)diethanone (4y). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53-8.50 (d, J = 3 Hz, 2H), 7.81 (s, 2H), 7.63-7.61 (m, 2H), 2.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 140.1, 130.1, 128.5, 126.4, 126.0, 30.9; Cl-MS *m/z* 230 [$(M + NH_4)^+$, 100]. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22, H, 5.70. Found: C, 79.18, H, 5.88.

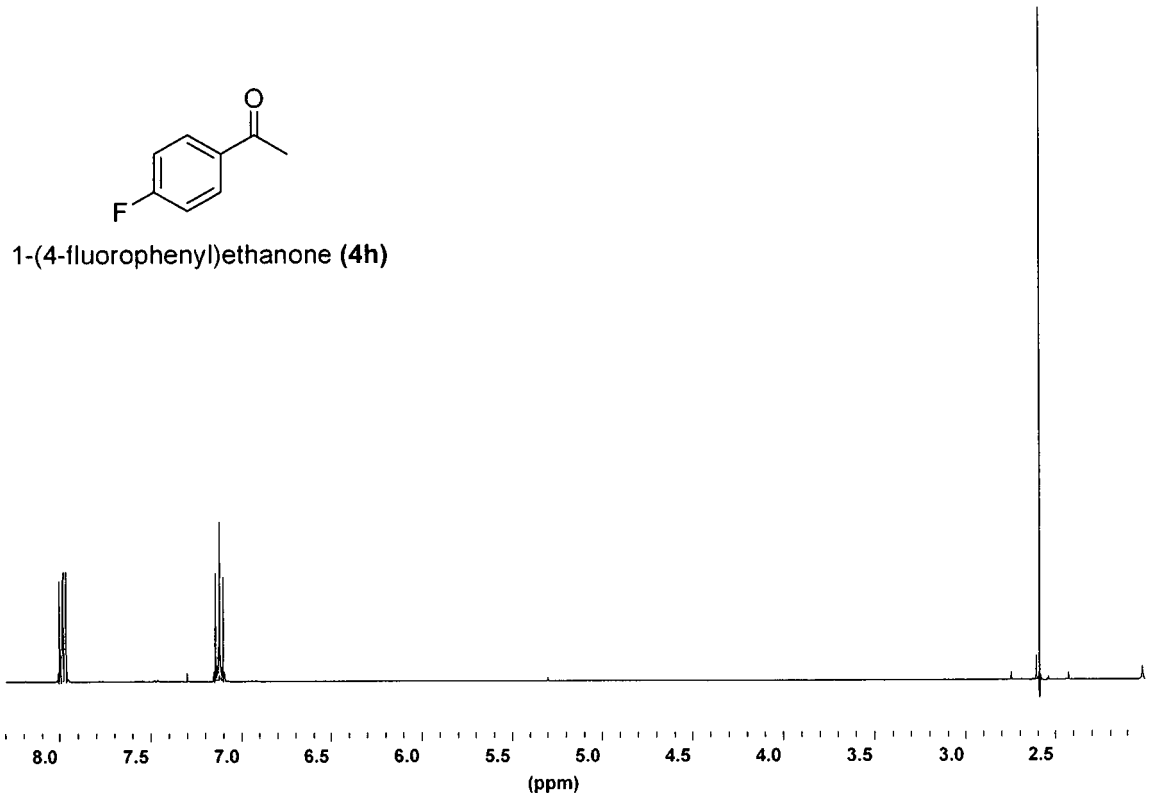
1-(Naphthalen-2-yl)propan-1-one (4ia). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.8 Hz, 1H), 7.99 (d, , J = 8.2 Hz, 1H), 7.89-7.87 (m, 3H), 7.54-7.42 (m, 2H), 3.02 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 136.0, 134.7, 133.9, 133.0, 130.0, 128.8, 128.3, 127.2, 126.3, 124.4, 32.3, 8.9; Cl-MS *m/z* 202 $[(M + NH_4)^+, 70]$, 185 $[(M + H)^+, 100]$; HRMS Calcd for $C_{13}H_{13}O$ $(M + H)^+$: 185.0966. Found: 185.0971. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75, H, 6.57. Found: C, 84.26, H, 6.49.

Propiophenone (4ie). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.57-7.53 (m, 1H), 7.49-7.43 (m, 2H), 3.01 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 137.3, 133.3, 129.0, 128.4, 32.2, 8.7; Cl-MS *m/z* 152 $[(M + NH_4)^+, 100]$, 135 $[(M + H)^+, 68]$; HRMS Calcd for $C_9H_{11}O$ $(M + H)^+$: 135.0810. Found: 135.0806. Anal. Calcd for $C_9H_{10}O$: C, 80.56, H, 7.51. Found: C, 80.30, H, 7.54.

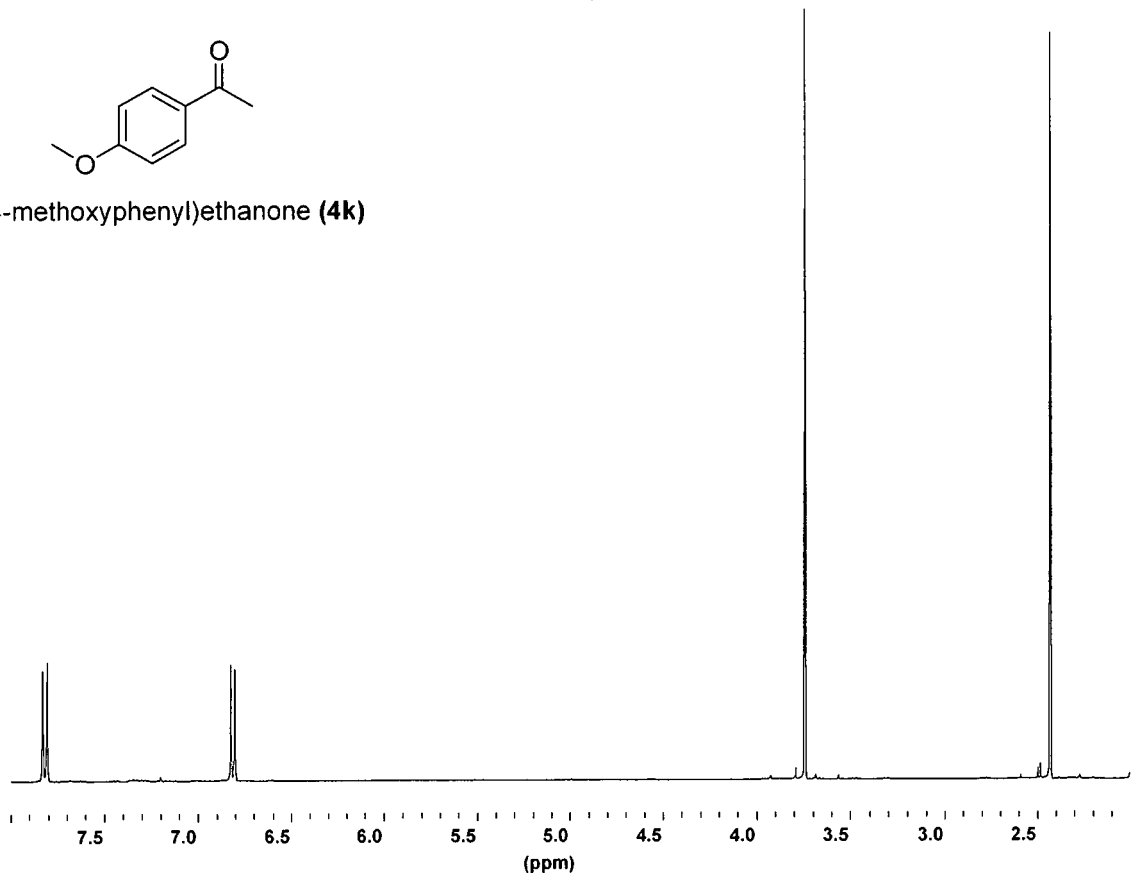
1-(4-Fluorophenyl)propan-1-one (4ih). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.92 (m, 2H), 7.06-7.02 (m, 2H), 2.90 (q, J = 7.2 Hz, 2H), 1.15(t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 166.0 (d, J_{CF} = 254 Hz), 133.7 (d, J_{CF} = 3.0 Hz), 131.0 (d, J_{CF} = 9.0 Hz), 116.0 (d, J_{CF} = 22 Hz), 32.1, 8.6; Cl-MS *m/z* 153 $[(M + H)^+, 67]$, 123 (100); HRMS Calcd for $C_9H_{10}FO$ $(M + H)^+$: 153.0716. Found: 153.0716. Anal. Calcd for for C_9H_9FO: C, 71.04, H, 5.96. Found: C, 72.27, H, 5.89.

4.6. Sample ^{1}H NMR spectra (400 MHz, $CDCl_3$)

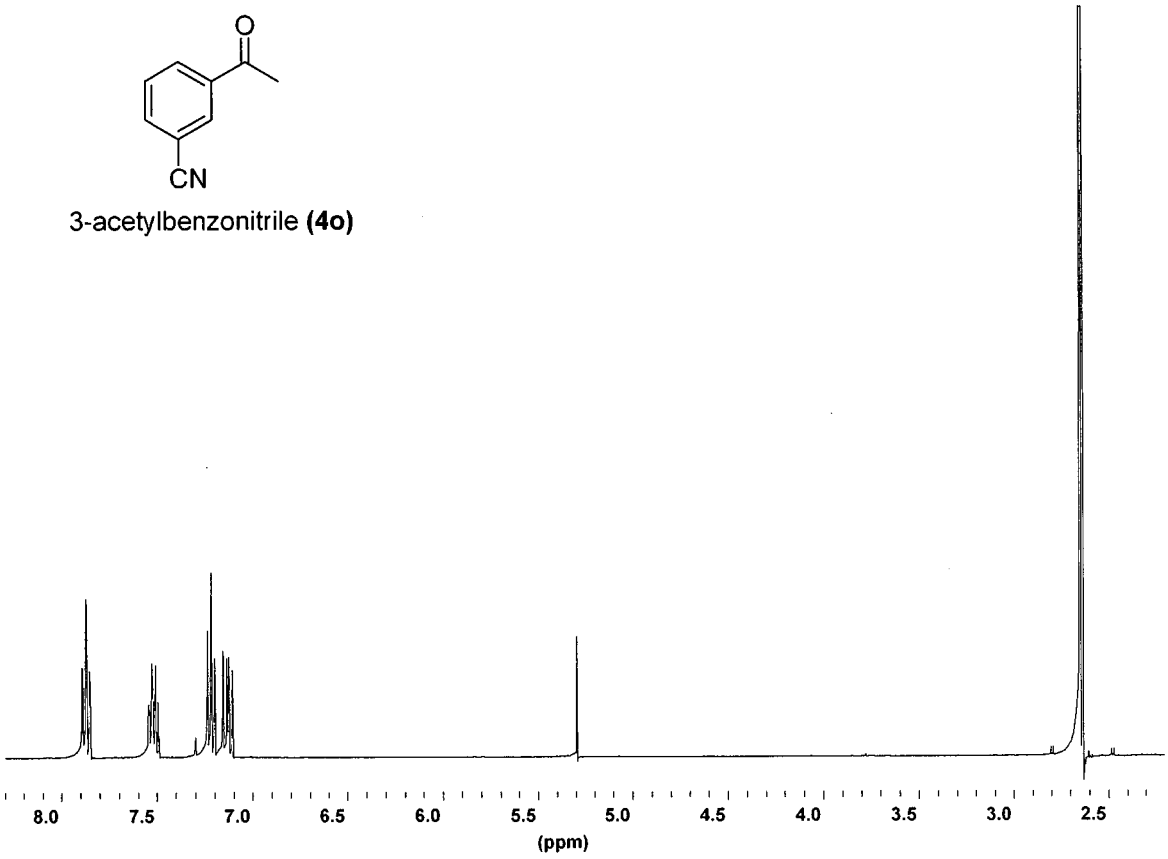
1-(4-fluorophenyl)ethanone **(4h)**



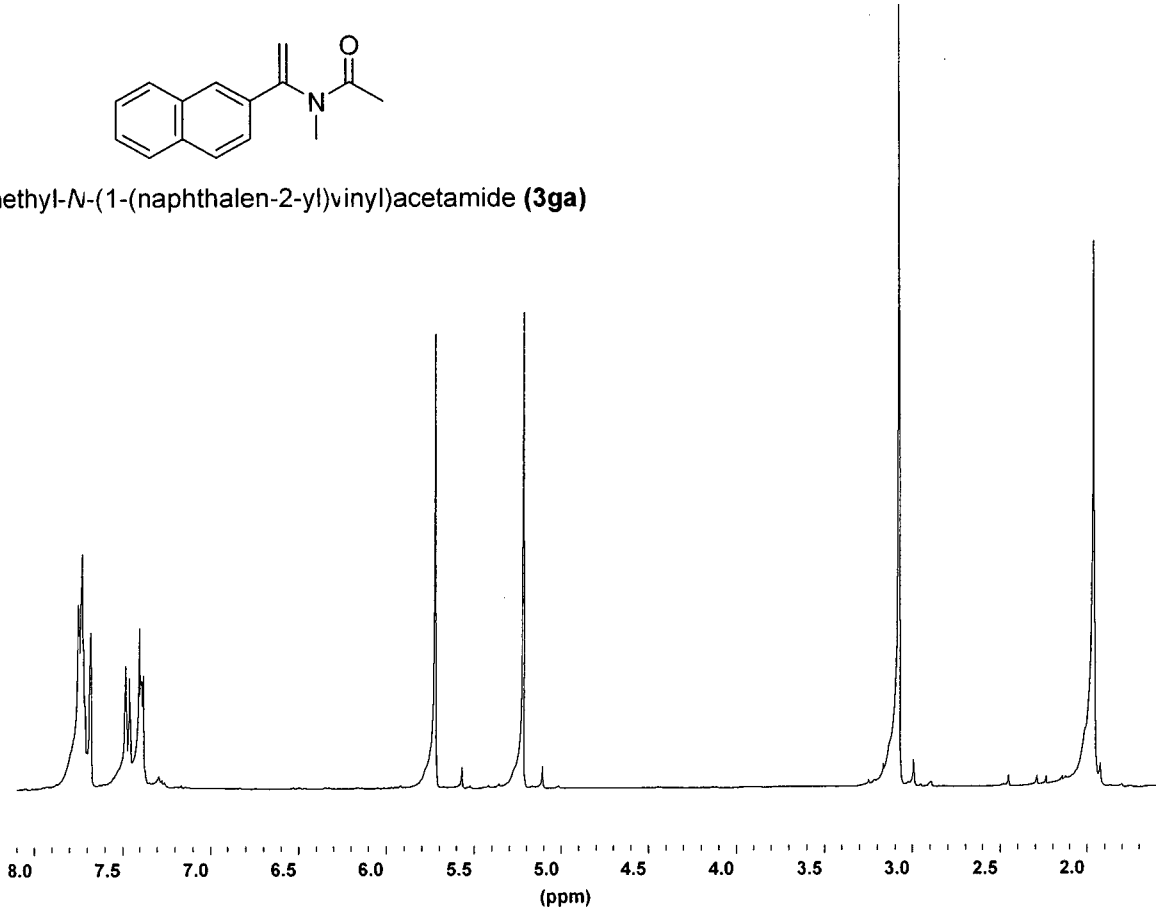
1-(4-methoxyphenyl)ethanone **(4k)**



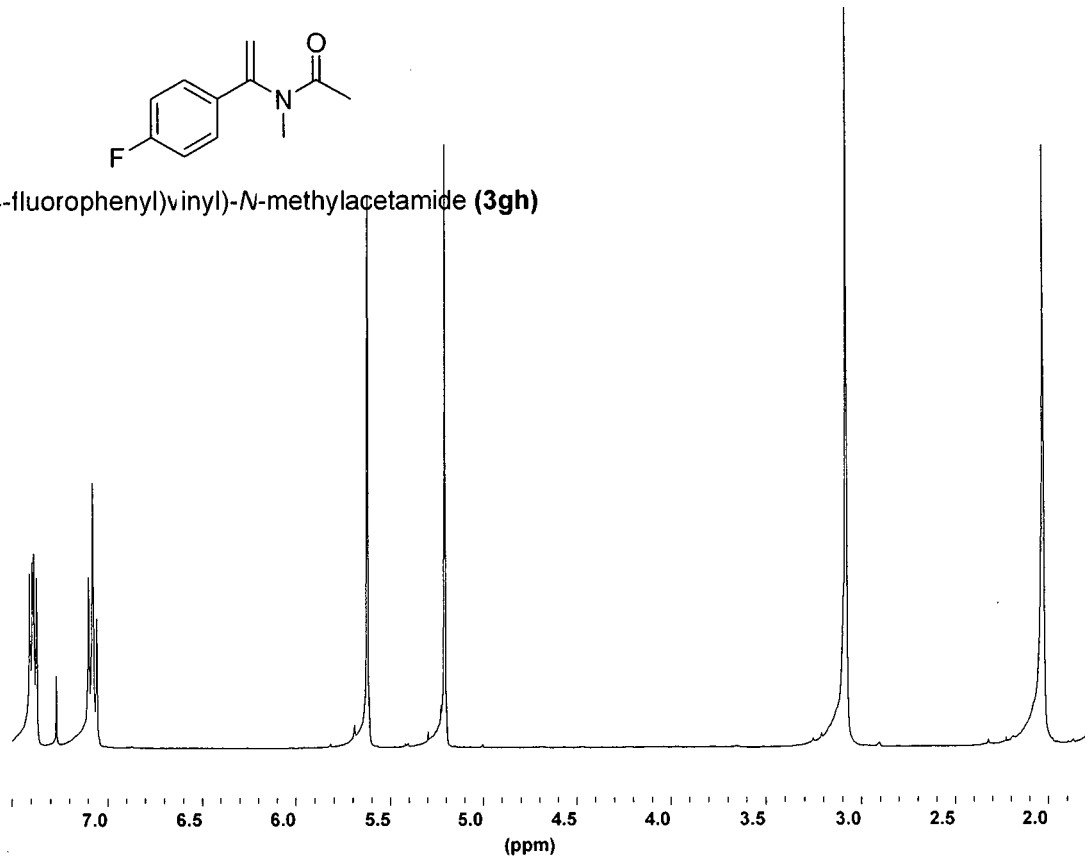
3-acetylbenzonitrile **(4o)**



N-methyl-*N*-(1-(naphthalen-2-yl)vinyl)acetamide **(3ga)**



N-(1-(4-fluorophenyl)vinyl)-*N*-methylacetamide **(3gh)**



CHAPTER FIVE

Regioselective Heck Arylation at Low Catalyst loadings

5.1. Introduction

The challenge of sustainability in modern chemistry will be met with new technologies and processes, provided significant progress is made in several key research areas, such as the expansion of chemistry to renewable feedstock, the design of environmentally benign chemicals and solvents, the minimisation of depletive resources, and the development of high-performance catalysis.[346] Since the conception of the carbon-carbon bond forming Heck reaction, in the late 1960s, most efforts have focussed on broadening the scope and understanding of the chemistry, and thus the mechanisms. Towards the latter end of the 20th century to present, attention has mainly been placed on making these types of reaction more economical, but also practical, yielding an attractive process leading towards a widespread applicability in industry.[21,347]

The high cost of palladium acts as a large deterrent, where the majority of catalyst systems require 1-5 mol% for effective coupling.[21] Heterogeneous catalysts offer facile recovery, and separation of catalyst and product through filtration which makes an attractive option over modern homogeneous catalysts. Considerably lower catalyst loadings, catalyst longevity, easy recovery and recycle, whilst achieving high TONs, would considerably improve the practicality of homogeneous catalysts (Chapter 1).[348]

Contamination of product usually by the metal also features quite highly on problems associated with organometallic catalytic reactions. The pharmaceutical industry must contain the level to below 10 ppm. Any Pd based process which

achieves TONs of 1 x 10^5–10^6 could in theory rid of cost and contamination issues together, an excellent feature for pharmaceutical and fine chemical applications.[348]

In 1995 Herrmann, Beller and coworkers observed the formation of palladium black in the reaction between 4-bromoanisole and *n*-butyl acrylate when a typical amount of $Pd(OAc)_2$ (1 mol%) and triphenylphosphine (2-6 mol%) were used, probably from the decomposition of the ligand through P-C_{aryl} bond cleavage after oxidative addition. Constant P-C_{aryl} cleavage depletes the system of phosphine, therefore decreasing catalyst stability. They were then to discover new, structurally defined, easy-to-handle palladium complexes surpassing all previously known catalysts of the Heck reaction with respect to stability and lifetime, in the shape of efficient palladacycle pre-catalyst (Figure 5.01).[349]

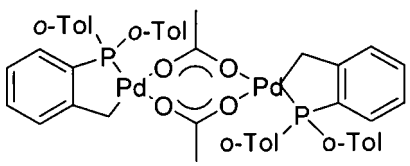


Figure 5.01. The first example of a palladacycle.

Very quickly, palladacycles research became a field of mounting interest, with many research groups introducing their own variants on the Herrmann-Beller palladacycle (HBP) prototype. Reports using these new HBPs were documenting TONs that were reaching higher and higher numbers. Large TONs were reported for some simple Heck and Suzuki couplings.[350-353] One such example is the Heck reaction of activated 4-bromobenzaldehyde and *n*-butyl acrylate using the palladacycle in Fig. 5.01, which produced a TON of 2 x 10^5 at a catalyst loading of 5 x 10^{-3} mol% after 10 hours.[349]

Palladacycles deserve a mention as their discovery paved the way for ultra-low loadings for C-C cross coupling reactions which had never been accomplished before. For the first time TONs of up to 1 x 10^6 were observed in the Heck coupling of *n*-butylacrylate with the electronically activated electron-deficient aryl bromide, 4-bromoacetophenone.[354] Later, it was realised that 4-bromoacetophenone may not be good indicator of catalyst activity, since palladium acetate in the absence of any additional ligands acheives TONs of up to 1 x 10^5 in coupling reactions with this substrate.[353] With the more electronically challenging electron-rich bromide, 4-bromoanisole, the maximum TON achieved was considerably lower at 630.[353,354] Still some controversy surrounds the exact mechanism of the Heck reaction conducted with palladacycles, whether the complexes remain quasiuncharged (in a Pd(II)/Pd(IV) process), or deliver a slow homeopathic amount of naked palladium to the reaction.[348]

The palladacycle in general can be applied to a number of coupling reactions, as demonstrated by Albisson and coworkers.[355] Fig. 5.02 depicts an orthopalladated triarylphosphite complex which was applied to the coupling of phenylboronic acid and 4-bromoacetophenone to furnish 1-(biphenyl-4-yl)ethanone, and accomplished TONs of 1 x 10^6 at 110 °C for 2 h in toluene. The formation of 4-methoxybiphenyl when the same boronic acid was coupled to 4-bromoanisole and produced TONs of 3 x 10^4 after 15 h at 130°C.

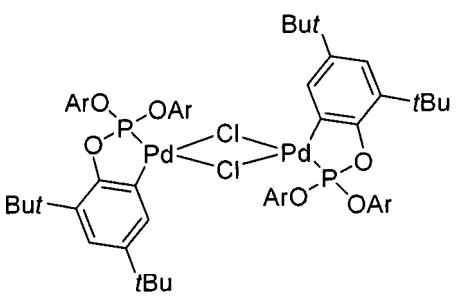
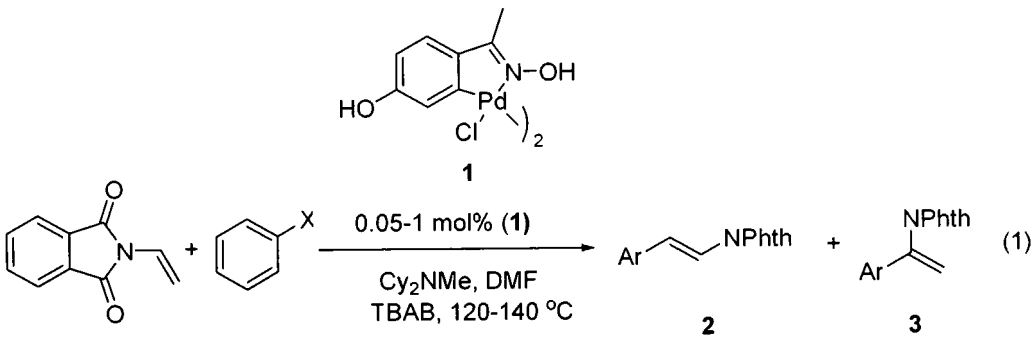


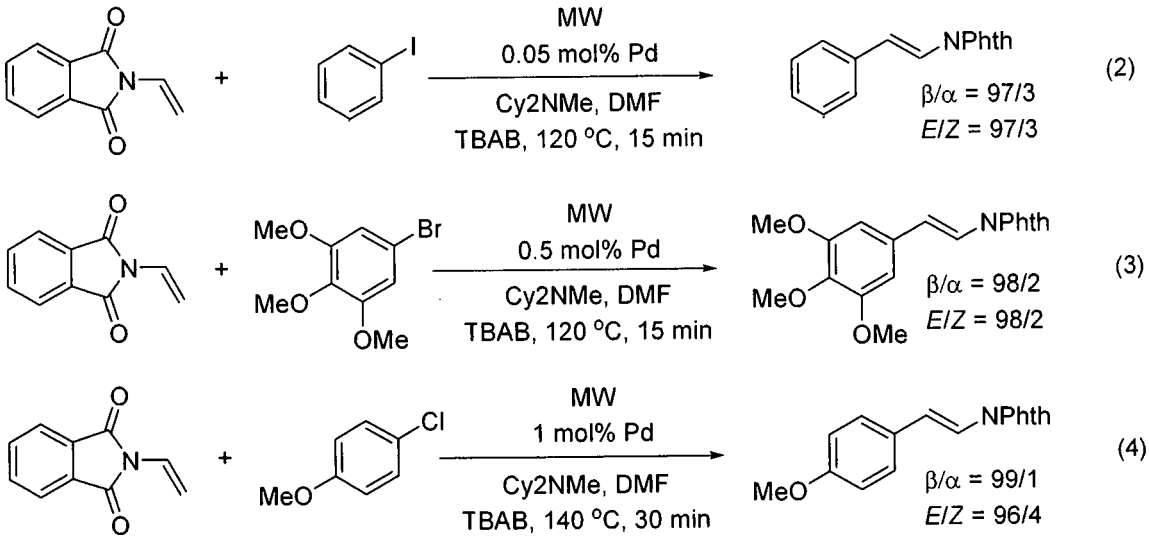
Figure 5.02. Triarylphosphite palladacycle.

The same palladacyle in Fig. 5.02 can also be applied to Heck couplings. When 4-bromoacetophenone was coupled to styrene, TONs of 5.75 x 10^6 could be reached at 180°C using a catalyst loading of 1 x 10^{-5} mol%, isolated within 69 h.[356]

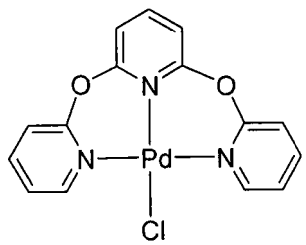
Very recently Nájeria and coworkers arylated *N*-vinylphthalimide at the β-position using aryl iodides, bromides and chlorides with palladium acetate or phenone oxime-derived palladacycles (**1**) as catalysts under phosphine-free conditions (Eq. 1).[357]



The reaction was successfully completed in organic solvents such as DMF in the presence of an organic base, such as dicyclohexylmethylamine (Cy_2NMe) with TBAB as additive. Some arylations could be completed within 15-30 min under microwave heating (Eq. 2-4), producing (*E*)-*N*-styrylphthalimides **2** with good regioselectivity over the branched product **3**.[357] Equations 2-4 are examples of the formation of the β-products, from iodides, bromides and chlorides, at palladium loadings as low as 0.05-1 mol% with palladacycle **1**. The yields of (*E*)-*N*-styrylphthalimide varied from fair to good. For equations 2, 3 and 4, the yields obtained were 65%, 67% and 66% respectively.



Ahn and coworkers showed that new palladium-containing pincer complexes (Eq. 5) composed of six-membered metallacycles (**4**) displayed exceedingly high catalytic efficiency, using catalyst loadings of as low as 1 x 10^{-7}mol% when coupling was applied to the arylation of methyl acrylate with iodobenzene in DMF (Eq 5).[358] A 14 h sample afforded a yield of 28%, and after 6 days a yield of 84% was obtained. A remarkably high TON of 8.4 x 10^{8} and TOF = 5.7 x 10^{6} h^{-1} were acheived. These represent the highest TONs reported so far for the Heck reaction.[358]



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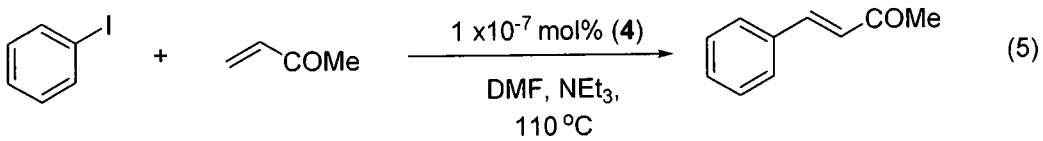


High TONs were also achieved by Uozumi and coworkers, who reported a novel NCN pincer palladium complex bearing pyrroloimidazolone groups. It was found to

catalyse the Heck reaction with high catalytic activity, showing a TON of approximately 5.2 x10^8 for the Heck reaction of aryl iodides with methyl acrylate in 1-methyl-2-piperidone (NMP) as solvent.[359]

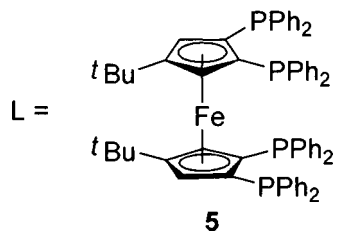
Santelli and coworkers postulated that the Pd center had to be strongly stabilised by up to 4 phosphine equivalents, regardless of the resting state of the catalyst, to inhibit decomposition from the Pd(0) species, which is probably involved in limiting the lifetime of the catalyst.[360] If the Pd centre could be kept highly coordinated, such decomposition may not take place (which is thought to be precipitation of inactive Pd particles in the form of Pd black). This was a very successful approach which led to the introduction of Tedicyp, a tetradentate ligand based on a cyclopentane alkyl backbone (Fig. 5.03) (also, see Chapter 2).

Figure 5.03. Tedicyp.

This tetraphosphine in combination with $[(\eta^3\text{-}C_3H_5)PdCl]_2$ affords a catalyst precursor which is amongst the most active in allylic substitution, Heck, Suzuki or Sonogashira-type reactions. TONS of up to 6.8 x 10^5 for allylic amination, 9.8 x 10^6 for allylic alkylation, 9.7 x 10^7 for Suzuki cross-coupling, 2.8 x 10^6 for Sonogashira alkynylation and 2.1 x 10^8 for Heck reaction have been obtained with this catalyst precursor.[301,360-369] The Tedicyp complex shows a stability which could be attributed to the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring, which probably increases the coordination of the ligand to the metal and therefore the catalyst longevity. The complex formed by association of Tedicyp with $[(\eta^3\text{-}C_3H_5)PdCl]_2$ seems to possess a fine balance of steric

and electronic properties, which allow fast catalytic processes with a very wide variety of substrates.[301,360-369] Of particular interest to us are the results of the Heck transformation with Tedicyp and $[(\eta^3\text{-}C_3H_5)PdCl]_2$, in which the coupling of 3,5-bis(trifluoromethyl)bromobenzene to *n*-butyl acrylate produced a TON of 2.1×10^8 at 130°C, after 72 h.[361] A 78% yield was obtained in 40 h for the same reaction in air, with a TON of 7.8×10^7. For arylation of *n*-butyl acrylate with more stubborn substrates, for example deactivated 4-bromoanisole, the TON was 8.2×10^4 after 72 h, with a 82% yield.[361]

The Heck reaction of vinyl bromides can be performed with a wide variety of alkenes such as acrylates, enones, styrene derivatives, sulfones or simple linear and cyclic alkenes.[370] A range of *E*- and *E*,*E*-1,3-dienes have been selectively prepared in good yields. Noteworthy are the high levels of regio- and stereoselection for most of the reactions, as well as the functional group tolerance. Most of these reactions can be performed with as little as 0.01–1 mol% catalyst using the same Tedicyp catalyst system.



5

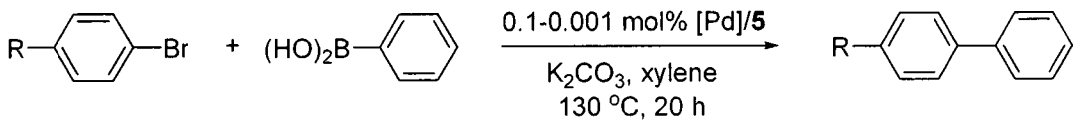
Figure 5.04. Ferrocenylphosphane ligand.

Ferrocenylphosphanes (Fig. 5.04) can also catalyse Heck and Suzuki at low catalyst loadings (Table 1).[371] For the Suzuki reaction, Hierso and coworkers found that employing the system $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ combined with ferrocenyltetraphosphane **5** gave an excellent catalytic system, which allowed aryl bromides to be coupled to

phenyl boronic acid with good TONs, achievable even with deactivated 4-bromoanisole.

The coupling of activated aryl bromides such as 4-trifluoromethylbromobenzene produced a TON of 1.5 x 10^5 and 1 x 10^5 (Entries 1 and 2), 4-bromoacetophenone (Entry 4) and 4-cyanobromobenzene (Entry 3) yielded TONs of 1 x 10^5, and deactivated 4-bromoanisole achieved a good TON of 7.7 x 10^4 and 1 x 10^4 (Entries 5 and 6). The coupling with aryl chlorides did not produce as higher TONs as their aryl bromide counterparts, even at loadings of 1 mol% Pd. For example the same reaction with activated 4-cyanochlorobenzene at 0.1 mol% Pd achieved a yield of 42%, and a TON of 420.[371]

Table 1. The Suzuki reaction using palladacycle **5.**

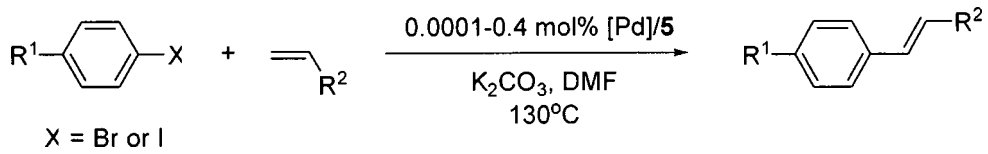


Entry	R	mol% cat.	Yield (%)	TONs
1	CF_3	1 x 10^{-4}	15	1.5 x 10^5
2	CF_3	1 x 10^{-3}	100	1 x 10^5
3	CN	1 x 10^{-3}	100	1 x 10^5
4	COMe	1 x 10^{-3}	100	1 x 10^5
5	OMe	1 x 10^{-3}	77	7.7 x 10^4
6	OMe	1 x 10^{-2}	100	1 x 10^4

Ligand **5** could also be successfully applied to the Heck vinylation of aryl iodides and aryl bromides (Table 2). The highest TON of 1 x 10^6 was found for the coupling of iodobenzene with *n*-butylacrylate (Entry 1), taking 48 h to complete with an

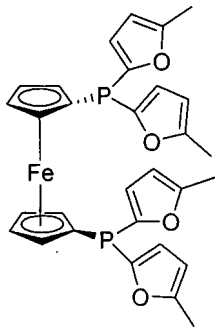
isolated yield of 100% at a catalyst loading of 1 x 10^{-4} mol% Pd. Ferrocenyl ligand **5** was applied to the reaction involving deactivated 4-bromoansiole which was coupled to *n*-butylacrylate at a catalyst loading of 1 x 10^{-2} mol% Pd (Entry 2) and then to styrene at 1 x 10^{-3} mol% Pd (Entry 3), which proceeded with high TONs of 1 x 10^4 in 48 h and 6.5 x 10^4 in 20 h, respectively. Electron-rich *n*-butyl vinyl ether was coupled to 4-bromobenzaldehyde at 0.1 mol% and 0.4 mol% palladium loadings (Entries 4 and 5), yielding TONs of 4.1 x 10^2 and 2.5 x 10^2, respectively.[346,371]

Table 2. The Heck reaction using ligand **5**

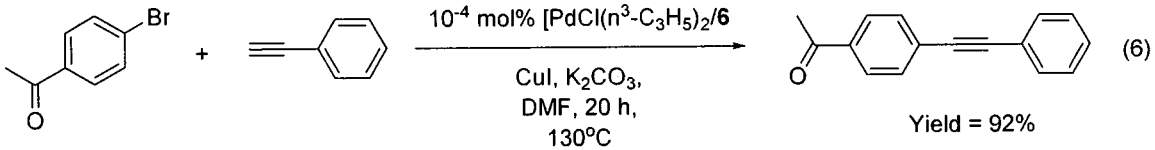


Entry	R^1	R^2	X	mol% cat.	Yield (%)	TONs
1	H	CO_2nBu	I	1 x 10^{-4}	100	1 x 10^6
2	OMe	CO_2nBu	Br	1 x 10^{-2}	100	1 x 10^4
3	OMe	Ph	Br	1 x 10^{-3}	65	6.5 x 10^4
4	CHO	*n*BuO	Br	0.1	41	4.1 x 10^2
5	CHO	*n*BuO	Br	0.4	100	2.5 x 10^2

Noteworthy is also the successful application of ferrocene incorporated into bis(difurylphosphino)ferrocene ligands which can also be useful for Suzuki, Heck and Sonogashira reactions, achieving high yields at low substrate to catalyst ratios. Depicted in Eq. 6 is a selected example of the Sonogashira reaction which utilises ligand **6** combined with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and copper iodide in DMF, featuring one of the highest reported TONs of 9.2 x 10^5 for Sonogashira coupling.[372]

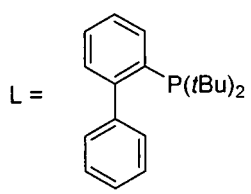


6

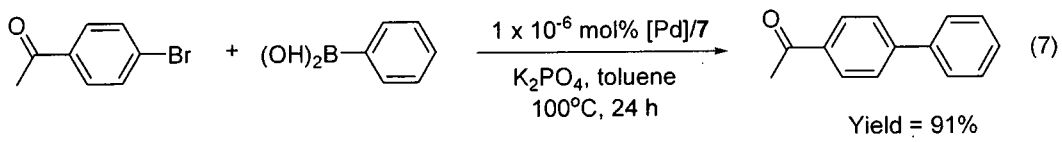


(6)

One of the lowest catalyst loadings reported in literature for the Suzuki cross-coupling reaction was carried out by Buchwald and coworkers[373] in the coupling of 4-bromoacetophenone with phenylboronic acid (Eq. 7) utilising 1 x 10^{-6} mol% Pd and ligand **7**, producing a TON of 9.1 x 10^7, although a control reaction conducted in the absence of phosphane ligands could be completed with 1 x 10^{-3} mol% $Pd(OAc)_2$, suggesting that reactions of this type of substrate combination are particularly facile.[355,374]



7



(7)

High TONs have been reported mostly for very simple systems, where virtually any Pd-containing catalyst displays high activity, *e.g.*, the Heck reaction of iodobenzene or activated aryl bromides with acrylates or styrene, or the Suzuki coupling of these halides with phenylboronic acid. Whilst palladacycles have been

tested in synthetically complex substrates, they have in no case enjoyed such high TONs (*vide supra*). It is clear that TONs reported for palladacycles sometimes exceed the TONs observed with traditional catalysts, often in significant ways, and this can be due either to the slow activation of the precatalyst, or due to the *in situ* formation of ligands that are stabilising in nature to some or all the intermediates in the catalytic cycle.[348] This is not to say that traditional catalyst systems could not produce similar TONs, even though in relation to thermal stability they may not offer the same characteristics as palladacycles.

Some studies suggest that a high TON is achievable with earlier systems. Spencer in 1983 published a thorough study on the TON of a typical Heck reaction using $Pd(OAc)_2/P(o\text{-}Tol)_3$ system, in the arylation of styrene, acrylates and acrylonitrile with aryl bromides. The TONs were all over 1×10^4 and reached, in one case, 1.3×10^5.[375]

Herrmann and coworker's extensive study on the pallacycle revealed that in the presence of a TBAB additive, both the Pd/PPh_3 and $Pd/(o\text{-}Tol)_3P$ systems produced TONs which were as high as those accomplished by ligandless Pd, attaining TONs of up to 1×10^6. So it does indeed seem possible, to achieve high TONs even with traditional Pd/triarylphosphane systems.[179]

De Vries and coworkers reported reasonably high TONs (*ca.* 3×10^3) in their study of the Heck reaction between *ortho* and *para* bromotoluene with ethylene, to yield the corresponding vinyl toluenes.[376] Recently, water-soluble triarylphosphanes bearing a carbohydrate moiety were shown to achieve TONs of 1×10^4 -10^5 in Suzuki[377-379] and Heck[378] couplings of activated systems, and this appears to be much better than the performance of the traditional Pd(0)/TPPTS ligands.

Traditional phosphites also have the ability to produce high TONs in Heck reactions and Suzuki couplings, where TONs of 1×10^4 and 1×10^5 were observed, respectively, although the reactions require a large ligand to Pd ratio. For the Heck reaction of deactivated aryl bromides, a conversion of 31% is observed at a loading of 1×10^{-3} mol% Pd.[380,381]

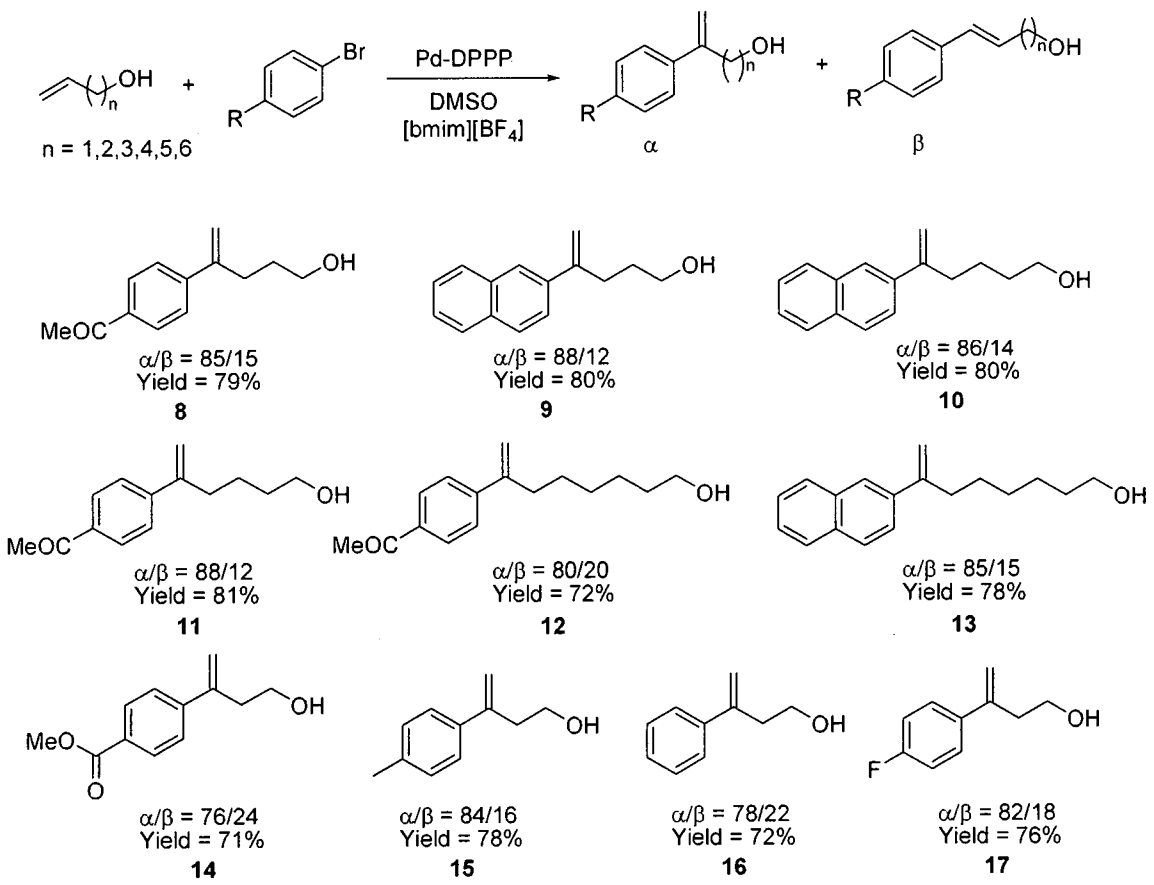
This concept of catalyst longevity in relation with stability of the catalytic species within the reaction is of key importance in order to achieve high TONs, but one also needs to ensure that the system works efficiently and regioselectivity must not be overlooked. Sustainable chemistry must also be recognised as a major factor when new processes for old reactions are discovered. The performance of palladacycles may be mimicked, at least in some cases, by dilute $Pd(OAc)_2$.[348] Industrial processes may not favour their use as much as originally thought.

As discussed in previous chapters, a large amount of focus has concentrated on Heck reactions involving electron-deficient olefins, and arylation at the internal position of the olefin double bond. However, for arylations of electron-rich olefins there seems to be little or no attention in improving TONs or catalyst loadings, as much interest has been placed on the invention of systems which provide a greener route than the reactions in molecular solvents, and most importantly, ensure regioselectivity.

Most examples of regioselective Heck arylations occur at 2.5-5.5 mol% Pd.[105,107,151,181-183,192-194,199,200,238] There are two examples in the literature, dealing with the regioselective arylation of electron-rich olefins, towards the internal α position of the double bond, at lower catalyst loadings. Both examples are from Xiao and coworkers.[104,200] The first features electron-rich unsaturated alcohols, which are

coupled to aryl bromides in an ionic liquid/DMSO solvent cocktail at a catalyst loading of 1 mol% palladium in a Pd/DPPP system (Scheme 5.01).

Selected examples, which are given in Scheme 5.01, illustrate the successful arylation of unsaturated alcohols of varying chain lengths with a range of aryl bromides after 24 h, with good to excellent regioselectivity towards the internal α position of the alcohol olefin bond. Products **8, 9** and **10** (and also **11, 12** and **13**) demonstrate the ease with which larger allylic alcohols can be coupled, and the coupling reaction with homoallylic alcohols (**14-17**) can tolerate a number of electron- withdrawing (**10** and **17**) and electron-donating (**15**) functionalities on the bromobenzene ring.



Scheme 5.01. Arylation of unsaturated alcohols with aryl bromides.

It is important to note that even though 1 mol% Pd may not seem low, there are two reports in the literature, describing the preferential internal arylation of allyl alcohols and homoallyl alcohol with 1-naphthyl triflate; complex mixtures were formed with the corresponding iodide, and these reactions took place at a 2.5 mol% Pd loading.[181,182]

The other example of the regioselective reaction of electron-rich olefins by aryl halides features the lowest catalyst loading ever documented, of 0.1% Pd from Xiao and coworkers (Eq. 8). Here, all products afforded complete regioselectivity towards the internal product (Table 3).

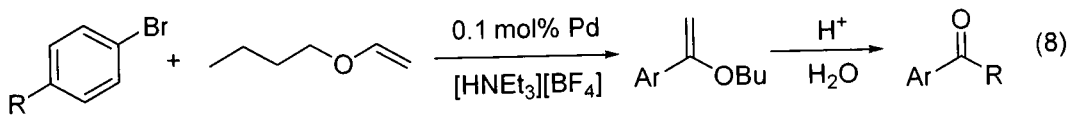
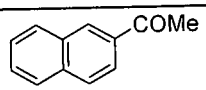
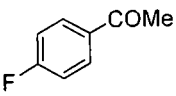
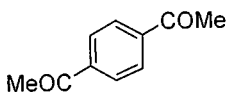
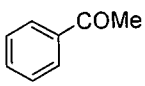
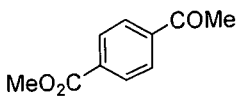
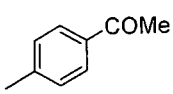


Table 3. Regioselective arylation at 0.1 mol% Pd[200]

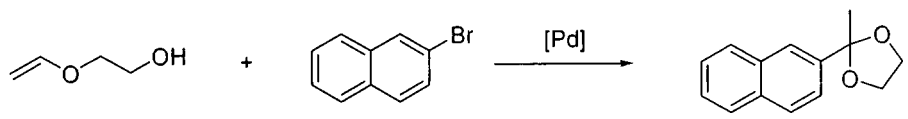
Entry	Product	Time (h)	Yield (%)
1		12	91
2		12	94
3		12	91
4		12	90
5		12	93
6		16	87

The arylation of *n*-butyl vinyl ether by aryl bromides at a low Pd loading is possible in ionic liquids, when promoted by $HNEt_3^+$ hydrogen bond donor salt, which

acts as an accelerator. The products can be furnished in 12-16 h, even with an electron donating -Me group (Entry 6), therefore producing TONs and TOFs values of up to 1000 and 83 h^{-1}, respectively. This result represents the highest TON values ever reported for the internal arylation of electron-rich olefins.

In the first chapter of this thesis, we discussed an ideal catalyst system as one which is inexpensive, can achieve a high selectivity and conversion at fast rates, and use with low catalyst loadings. Throughout this thesis we have shown the progression from ionic liquids, isopropanol to ethylene glycol, displaying the importance of a good hydrogen-bond donor with a high E_T^N, showcasing the exceptional abilities of common cheaper solvents which may have been overlooked in the past. Table 4 presents a comparison of the effect of solvent and catalyst loadings of electron-rich **2a**.

Table 4. Effect of solvent on the regioselective Heck arylation of 2-hydroxy ethyl vinyl ether on the rate



1e **2a** **3ea**

>99/1 regioselectivity

Solvent	Catalyst loading (mol%)	Time (h)	Reference
Ionic liquid	3.0	8	Chapter 2
Isopropanol	4.0	5	Chapter 3
Ethylene glycol	5.0	2	Chapter 4
Ethylene glycol (pre-mixing)	1.0	0.33	Chapter 4

The adapted procedure which was discovered to reduce the time of reaction dramatically (Chapter 4) also allowed for the catalyst loading to be reduced to 1.0

mol% Pd. The aim in this chapter is to improve the procedure in terms of reducing the palladium loading to a fraction of what has been reported in the past.

In this chapter, we report an extension of the ethylene glycol system in the arylation of electron rich olefins by aryl bromides using catalyst loadings of as low as 0.002 mol% Pd, without recourse to halide scavengers, the use of triflates, bulky phoshine ligands or expensive ionic liquid. To the best of our knowledge, these are the first known examples of the Heck reaction with this family of olefins at such a low loading. Moreover, due to the high price of palladium, the practical advantage of such low catalyst loading reactions can become increasingly important for industrial processes.

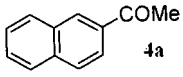
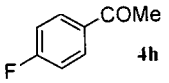
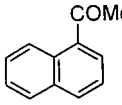
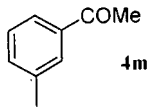
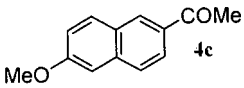
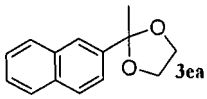
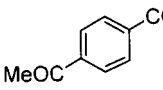
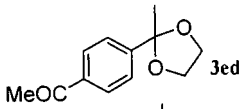
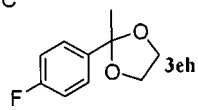
5.2. Results and Discussion

As already encountered from Chapter 4, ethylene glycol allows operation at just 1 mol % palladium at extremely fast times, following pre-mixing for a matter of 3-4 minutes after which the olefin is added sequentially. This offers the fastest times for the arylation of electron rich olefins. We believe that both the oxidative addition and olefin insertion step is facilitated by this action onto the ligand-bound Pd(0) complex. The next stage in our studies was to investigate the possibility of lowering the loading without compromising the rate of reaction. To examine feasibility, **1a** (1 mmol) was first arylated with **2a** (3 equiv.), at a palladium loading of 10^{-1} mol %, DPPP (0.2 mol %), NEt_3, 2 mL ethylene glycol at 145°C. A stock solution was prepared for this reaction, to maintain accuracy. Delightedly, the reaction furnished the coupled product in just 0.5 h, affording an 86% yield (Entry 1, Table 5).

Generally, all reactions required 0.5-1 h times to complete and the coupling of olefin **1a** was achieved in high yields, and fast times of 0.5 h (Entries 1-6) . The

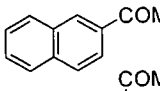
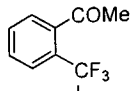
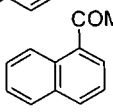
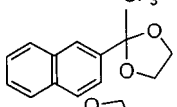
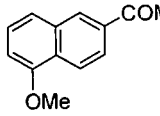
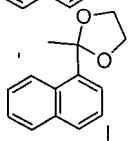
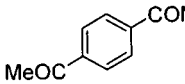
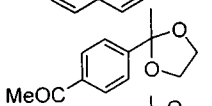
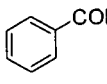
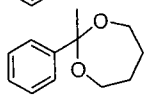
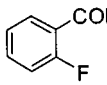
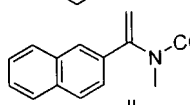
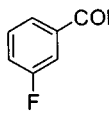
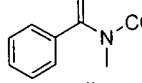
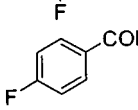
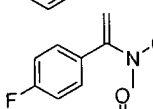
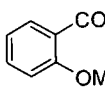
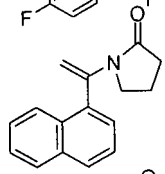
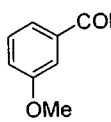
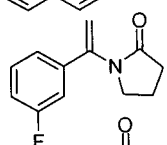
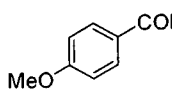
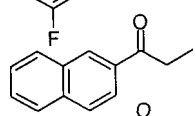
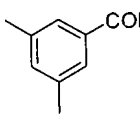
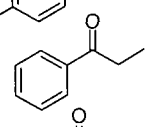
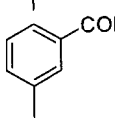
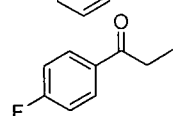
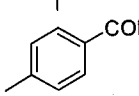
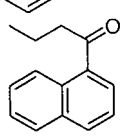
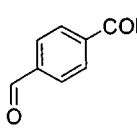
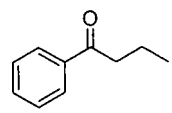
reaction could also be performed with relative ease in just 1 h, addition of acid was not required to promote ring closing.[192] Selected examples are shown in Table 5. However substrates containing strongly electron-donating groups in the *para* position (**2k** and **2n**) proved problematic in the arylation of **1e** in ethylene glycol, and the production of ketal was found to be sluggish. This has been the case throughout the course of these experiments in ethylene glycol when the ketalisation is attempted with these compounds. However, the coupling of **2k** and **2n** with **1a** can be executed quite straightforwardly (see Chapter 4), albeit slower then those which have an electron-withdrawing functionalities. Oxidative addition is probably made more cumbersome with electron-donating functionalities in the *para* position.

Table 5. Regioselective Heck at low catalysts loadings[a]

Entry	Olefin	S/C	Product	Time (h)	Yld (%)	Entry	Olefin	S/C	Product	Time (h)	Yld (%)
1	**1a**	1000	 **4a**	0.5	86	6	**1a**	1000	 **4h**	0.5	88
2	**1a**	1000	 **4b**	0.5	91	7	**1a**	1000	 **4m**	0.5	92
3	**1a**	1000	 **4c**	0.5	94	8[b]	**1e**	1000	 **3ea**	0.5	89
4	**1a**	1000	 **4d**	0.5	87	9[b]	**1e**	1000	 **3ed**	1	85
5	**1a**	1000	 **4e**	0.5	85	10[b]	**1e**	1000	 **3eh**	0.5	84

[a]Reaction conditions: 3.0 equiv. **1**, 1.0 mmol **2**, 1:2 $Pd(OAc)_2$:DPPP, and 2.5 equiv NEt_3 in 2 mL ethylene glycol at 145 °C; 100% conversion and no linear products; Isolated yields; **4** was obtained after acidification of **3**. [b]Conditions were the same as for [*a*], omitting aqueous acidic work up.

Table 6. Regioselective Heck reaction at lower catalyst loadings[a]

Entry	Olefin	S/C	Product	Yld (%)	Entry	Olefin	S/C	Product	Yld (%)
1	**1a**	5×10^5	 **4a**	75	16	**1a**	1×10^5	 **4s**	72
2	**1a**	5×10^5	 **4b**	69	17[b]	**1e**	5×10^5	 **3ea**	67
3	**1a**	5×10^5	 **4c**	67	18[b]	**1e**	5×10^5	 **3eb**	75
4	**1a**	5×10^5	 **4d**	71	19[b]	**1e**	5×10^5	 **3ed**	70
5	**1a**	5×10^5	 **4e**	71	20[b]	**1f**	1×10^5	 **3fe**	73
6	**1a**	1×10^5	 **4f**	75	21[b][c]	**1g**	1×10^4	 **3ga**	74
7	**1a**	1×10^5	 **4g**	73	22[b][c]	**1g**	1×10^4	 **3ge**	78
8	**1a**	1×10^5	 **4h**	72	23[b][c]	**1g**	1×10^4	 **3gh**	76
9	**1a**	1×10^5	 **4i**	76	24[b][c]	**1h**	1×10^4	 **3hb**	67
10	**1a**	1×10^5	 **4j**	75	25[b][c]	**1h**	1×10^4	 **3hg**	70
11	**1a**	1×10^5	 **4k**	72	26[b]	**1i**	1×10^5	 **3ia**	71
12	**1a**	1×10^5	 **4l**	70	27[b]	**1i**	1×10^5	 **3ie**	64
13	**1a**	1×10^5	 **4m**	71	28[b]	**1i**	1×10^5	 **3ih**	65
14	**1a**	1×10^5	 **4n**	73	29[b]	**1j**	1×10^4	 **3jb**	69
15	**1a**	1×10^5	 **4q**	74	30[b]	**1j**	1×10^4	 **3je**	73

[a]Reaction conditions: 3.0 equiv. **1**, 1.0 mmol **2**, 1:2 $Pd(OAc)_2$:DPPP, and 2.5 equiv NEt_3 in 2 mL ethylene glycol at 145 °C; 100% conversion and no linear products; Isolated yields; **4** was obtained after acidification of **3**. Reaction were run for 24 h. [b]Conditions were the same as for [*a*], omitting aqueous acidic work up. [c]No pre-mixing.

The remarkable feature regarding these reactions is that for catalyst loadings of up to 0.1 mol% Pd, they are executed with the production of minimal side products, allowing separation via a small silica plug. As the arylation showed promising results at lower catalyst loadings, we decided to improve the method by further reducing the Pd content, and expand the scope of substrate.

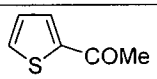
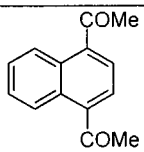
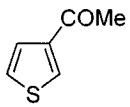
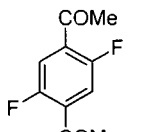
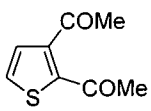
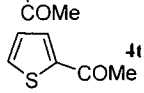
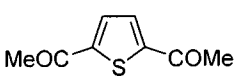
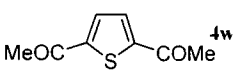
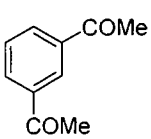
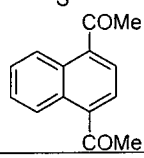
The catalyst loading was taken down two orders of magnitude to 1 x 10^{-3} mol % Pd (Table 6). Subsequent stock solutions were prepared to obtain lower loadings. As we are now dealing with small catalyst loadings, we deemed it more appropriate to use substrate/catalyst ratios (S/C) rather then percentages. To maintain accuracy when using small catalyst loadings, a stock solution was made, from which further dilutions were prepared. Initial results with the coupling of **2a** with **1a** showed that indeed the reaction was possible, although necessitating longer times for completion (24 h) (Entry 1, Table 6). The successful arylation of **1a, 1e, 1f, 1h, 1i** and **1j** was then performed with a range of aryl bromides containing both electron-donating (Entries 9-14) and electron-withdrawing (Entries 4, 6-8, 15-17, 19, 23 and 28). Of particular interest is the successful arylation with 2-substituted olefins **1i** and **1j**. Arylations carried out at lower loadings seem to generate lower yields, even though regioselectivity was maintained.

Some reactions did not benefit from pre-mixing, such as the enamides. In fact, pre-mixing for 4 minutes before adding the olefin surprisingly produced a mixture of the desired product **3g**, but also the ketal **3e**. This would indicate that ethylene glycol may act as a reactant after coupling of the enamide. This is not observed with any other olefin other then **3g**. Pre-mixing for longer times did not furnish the ketal alone, nor the enamide **3g**, a mixture was still produced. The problem was overcome simply

from omitting the pre-mixing process and adding all reactants at once and flushing with nitrogen.

To test the tolerance of the system further, the arylation with heterocycles was tested (Table 7). We were delighted to find that bromothiophenes could be easily coupled to **1a**, yielding the corresponding regioselective thiophene ketones **4t** and **4u** (Entries 1 and 2), with no sign of the linear product. Interestingly, dibrominated thiophenes could also be successfully arylated in very short times of just 0.5-1 h (Entries 3 and 4). The Xiao group were the first to demonstrate the regioselective arylation of heteroaryl halides to yield acetyl heterocycles in ionic liquid, but the reactions took 30 h.[106] For entries 3 and 4, high yields of 89% and 85% for products **4v** and **4w** were achieved, respectively.

Table 7. Arylation of dibromides and thiophenes[a]

Entry	Olefin	S/C	Product	Time (h)	Yld (%)	Entry	Olefin	S/C	Product	Time (h)	Yld (%)
1	**1a**	1000	 **4t**	0.5	91	6[b]	**1a**	1000	 **4y**	1	84
2	**1a**	1000	 **4u**	1	88	7[b]	**1a**	1000	 **4z**	0.5	90
3[b]	**1a**	1000	 **4v**	1	89	8	**1a**	100000	 **4t**	18	72
4[b]	**1a**	1000	 **4w**	0.5	85	9[b]	**1a**	100000	 **4w**	18	75
5[b]	**1a**	1000	 **4x**	1	86	10[b]	**1a**	100000	 **4y**	18	76

[a]Reaction conditions: 3.0 equiv. **1**, 1.0 mmol **2**, 1:2 $Pd(OAc)_2$:DPPP, and 2.5 equiv NEt_3 in 2 mL ethylene glycol stock solution at 145 °C; 100 % conversion and no linear products; Isolated yields; **4** was obtained after acidification of **3**. [b]Conditions were the same as for [*a*], 6.0 equiv. of **1** were used.

In Table 7, dibromides **2x, 2y and 2z** were also regioselectively arylated in 0.5-1 h. Entries 8-10 show the remarkable results obtained from the arylation of **2y, 2w** and **2y**, at a S/C ratio of 1 x 10^5. The reaction times were much longer which is to be expected; however it proves that the arylation can be performed to furnish products at low catalyst loadings regioselectively.

It is possible that the thermal stability of the Pd/DPPP system is attributed to the ethylene glycol, which may act as a ligand and inhibit decomposition of the catalyst, into inactive Pd(0). Santelli postulated if the Pd center was strongly stabilised by up to 4 phosphine equivalents, regardless of the resting state of the catalyst, decomposition from a Pd(0) species is inhibited, which otherwise limits lifetime of the catalyst.[360] If the Pd centre is highly coordinated, such decomposition may not take place, which may be the reason why palladacycles can perform under extremely low catalyst loadings.[301,346,349,350,353,361,363,365,369,382]

The danger when carrying our regioselective Heck reactions in dilute Pd solutions is that naked Pd may catalyse the arylation in a "ligand free" reaction, producing the linear product.[357,383] This observation was actually seen in the early stages of this study, where the solutions may not have been made completely homogeneous, and most of the DPPP was unable to bind to the Pd. Once the stock solution containing Pd/DPPP had been heated for 24 h at 60 °C, no linear product was seen.[384]

One possibility for the excellent performance of ethylene glycol in regiocontrol at extremely low loadings, is the ability for ethylene glycol to act as a hydrogen bond donor.[200] The surrounding environment is saturated with potential hydrogen-bond donors which have a rate accelerating effect, and the reaction can proceed rapidly at loadings of 0.01 mol% Pd, in the arylation of many aryl bromides. The highest TON (based on the isolated yield) recorded for these reactions is 3.75 x 10^5, or a TOF of 15

625 h^{-1} for the arylation of *n*-butyl vinyl ether **1a** and 2-bromonapthlene, **2a**. For heterocycles, in particular 2-bromothiphene **2t**, the TON of 910 is not as remarkable as the TOF which is 1 820 h^{-1}. Even the sterically hindered dibromide **2z** which has a TON of 900 achieves a TOF of 1 800 h^{-1}. To obtain TONs and TOFs like these without the use of triflates, halide scavengers, expensive ligands or solvents for the arylation of electron-rich olefins provides an efficient, viable route to the synthesis of enamides, substituted ketones, ketones and ketals at extremely low catalyst loadings. These TONs represent the lowest ever recorded for this family of olefins.

5.3. Conclusion

We have shown that a simple catalytic system employing $Pd(OAc)_2$ and DPPP in ethylene glycol allows the Heck reaction of electron-rich olefins to be run at very low catalyst loadings. Generally in complex synthetic situations, few catalysts achieve TONs of 1 x 10^3 in Heck or other cross-coupling reactions.[347,385-387] For successful reactions in industry, key factors need to be considered: cost, purification, throughput and time.

Reported here are the highest TONs recorded for the arylation of electron-rich olefins with aryl bromides, and provides a straightforward route to the synthesis of ketals, methyl ketones, substituted ketones and enamides. The aryl halides which can act as coupling partners in this system can range from heterocycles (**4t, 4u, 4v** and **4w**), or aryls containing various functionalities (electron withdrawing or donating) (*e.g.* **4d** or **4n**), or be sterically hindered (*e.g.* **4b**). Fast arylation can also occur at low catalyst loadings, some reactions completing in only 0.5 h at 0.1% Pd loading, comparable to those carried out under microwave heating. A particularly remarkable

result is the coupling of substituted electron-rich olefins **1i** and **1j**, which gave TONs of 7.1×10^4 and 7.3×10^3, respectively.

The lowest recorded Pd loading for the arylation of electron-rich olefins was reported by the Xiao group, in the coupling of **1a** with aryl bromides at 0.1 mol% Pd in ionic liquids, in the presence of a hydrogen-bond donor salt. The reaction completed in 12 h. The same reaction in ethylene glycol can be completed in 0.5 h, with no need for salt additives or triflates.

Homogeneous catalysis will only be able to compete successfully with classical organic chemistry for the production of fine chemicals when it shows clear advantages. In our work in ethylene glycol, we have lowered the cost by reducing the amount of catalyst, dramatically reduced the amount ligand, reduced side reactions, and maintained selectivity. Ethylene glycol also provides a greener alternative to organic or halogenated solvents.[347] The system requires no use of expensive or toxic silver of thallium halide scavenger salts, no triflates, or ionic liquids.

5.4. Experimental Section

General

All reactions were carried out under a nitrogen atmosphere. The olefins **1**, aryl halides **2**, $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (DPPP), triethylamine, and all solvents were purchased from Lancaster and Aldrich and were used as received. Chromatographic purifications were performed through a silica gel (mesh 230-400) plug for the ketals **3** and ketones **4**, and by the flash technique for the enamides **3** and subsituted ketones **3**. ^1H and ^{13}C NMR spectra were recorded on a Gemini 400 spectrometer at 400 (^1H) and 100 MHz (^{13}C) in ppm with reference to TMS internal standard in $CDCl_3$. Mass spectra were obtained by chemical ionisation (CI). The products were satisfactorily characterised by ^1H and ^{13}C NMR, MS, HRMS and in most cases elemental analysis. When possible, comparison of NMR spectra has been made with available literature data including our previous data. [105,107,199,200] Compounds **4i** [4079-52-1][319.320], **4l** [5379-16-8][388], **4q** [3457-45-2][389], **4s** [17408-14-9][388], **3jb** [2876-62-2][390] **3je** [495-40-9][391], **4w** [4927-10-0][392] and **4u** [1468-83-3][393] have all been reported previously.

General procedure for Heck arylation at lower catalyst loadings. The same procedure was used as for the reactions in ethylene glycol at 145 °C; however, the olefin 1 was added after 2-4 minutes of pre-mixing at 145 °C. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. A small sample was then taken for NMR analysis. Hydrolysis was carried out if required. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layer was washed with water until neutrality, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Isolated products(**4** and **3e** and **3f**) were extracted using a silica plug, yields of which are given in Table 3, 4 and 5 of the text. Products

3 or taking place requring S/C ratios greater then 1000 were purified via the flash technique using a 100 mL column over silica gel (mesh 230-400). An eluant of petroleum ether/ethylacetate (1:4) was used.

A stock solution of 0.1 mol% (1 mmol, 2mg) palladium together with 0.2 mol% DPPP (2mmol, 8mg) was prepared in 10 mL degassed ethylene glycol, which was used as the mother solution to which subsequent dilutions were made. To ensure the mixture was homogeneous, the solution was left stirring under nitrogen at 60°C for 12 hours. The solution turned a deep orange, with no sign of residue indicating that the catalyst/DPPP was disolved and homogeneous. To make a 1×10^{-2} mol% stock solution, 1 mL was taken from this mother solution and added (under nitrogen) to 9 mL of degassed ethylene glycol. This procedure was followed to make more dilutions, until the lowest catalyst loading was achieved of 1×10^{-3} mol%. Stock solutions of higher catalyst loadings maintained stability for a week, however solutions of lower loadings were prepared on the day the reactions were carried out.

5.5. Analytical data

1-(2-Methoxyphenyl)ethanone (4i). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.71 (d, J = 5.8 Hz, 1H), 7.45-7.41 (m, 1H), 7.01-6.93 (m, 2H), 3.92 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 165.1, 134.1, 131.7, 121.0, 111.2, 53.9, 32.2. Cl-MS *m/z* 168 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_9H_{10}O_2$ $(M + H)^+$: 151.0205. Found: 151.0201. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98, H, 6.71. Found: C, 71.88, H, 6.74.

1-(3,5-Dimethylphenyl)ethanone (4l). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 2H), 7.03 (s, 1H), 2.41 (s, 3H), 2.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 137.1, 136.5, 133.6, 125.1, 25.5, 20.0. Cl-MS *m/z* 166 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_{10}H_{16}NO$ $(M + NH_4)^+$: 167.0228. Found: 167.0226. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04, H, 8.16. Found: C, 80.93, H, 8.18.

4-Acetylbenzaldehyde (4q). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H) 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 192.8, 141.2, 137.3, 130.2, 129.4, 30.4. Cl-MS *m/z* 193 (100) 148 (30); HRMS Calcd for $C_9H_{12}NO_2$ $(M + NH_4)^+$: 166.0868. Found: 166.0872. Anal. Calcd for $C_9H_8O_2$: C, 72.96, H, 5.44. Found: C, 72.87, H, 5.68.

1-(2-Trifluoridemethyl)phenyl)ethanone (4s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.40 (m, 1H), 7.62-7.48 (m, 2H), 7.73-7.69 (m, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 140.8 (d, J_{CF} = 2.0 Hz), 132.3, 128.1, 127.3, 127.1, 125.3, 122.7, 31.0. Cl-MS *m/z* 206 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_9H_{11}F_3NO$ $(M + NH_4)^+$: 206.0793. Found: 206.0795. Anal. Calcd for $C_9H_{11}F_3NO$: C, 57.45, H, 3.75. Found: C, 57.42, H, 3.73.

1-(Thiophen-3-yl)ethanone (4u). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.04 (m, 1H), 7.55 (d, J = 4 Hz, 1H) 7.28 (d, J = 3 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 192.7, 143.1, 132.8, 127.4, 126.8, 28.0. Cl-MS *m/z* 144 [$(M + NH_4)^+$, 100] 127 (67); HRMS Calcd for C_6H_7SO $(M + H)^+$: 127.0218. Found: 127.0220. Anal. Calcd for C_6H_6SO: C, 57.10, H, 4.76. Found: C, 57.30, H, 4.78.

1,1'-(Thiophene-2,3-diyl)diethanone (4v). ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 5 Hz, 1H), 7.18 (d, *J* = 5 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.2, 191.7, 132.8, 130.9, 128.8, 127.4, 30.7, 29.5. Cl-MS *m/z* 172 [$(M + NH_4)^+$, 62] 186 (70) 155 (100); HRMS Calcd for $C_8H_{12}SO_2N$ $(M + NH_4)^+$: 186.0589. Found: 186.0592. Anal. Calcd for $C_8H_8SO_2$: C, 57.18, H, 4.76. Found: C, 57.18, H, 4.79.

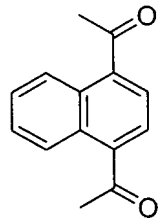
1,1'-(1,3-Phenylene)diethanone (4x). ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.20-8.17 (m, 2H), 7.59-7.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 137.8, 133.2, 129.5, 128.9, 27.1. Cl-MS *m/z* 180 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_{10}H_{14}O_2N$ $(M + NH_4)^+$: 180.1045. Found: 180.1023. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06, H, 6.21. Found: C, 73.83, H, 6.24.

1,1'-(2,5-Difluoro-1,4-phenylene)diethanone (4z). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.61 (t, *J* = 2Hz, 2H), 2.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 157.9 (d, J_{CF} = 249 Hz), 130.4(d, J_{CF} = 3.0 Hz), 119.1 (d, J_{CF} = 9 Hz), 31.7. Cl-MS *m/z* 216 [$(M + NH_4)^+$, 55] 195(100); HRMS Calcd for $C_{10}H_{12}F_2O_2N$ $(M + NH_4)^+$: 216.0836. Found: 216.0838. Anal. Calcd for $C_{10}H_8F_2O_2$: C, 61.22, H, 4.08. Found: C, 59.72, H, 4.21.

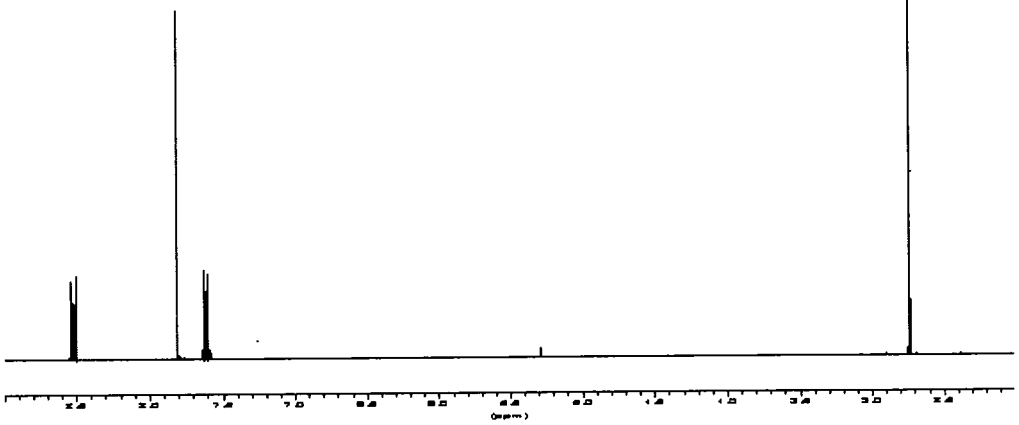
1-(Naphthalen-1-yl)butan-1-one (3jb). ^1H NMR (400 MHz, $CDCl_3$) δ 8.59-8.56 (m, 1H), 7.96-7.93 (m, 1H), 7.89-7.80 (m, 2H), 7.59-7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 134.4, 132.7, 130.5, 128.3, 128.2, 127.6, 126.1, 125.7, 124.8, 23.8, 14.70, 11.9. Cl-MS *m/z* 216 [$(M + NH_4)^+$, 65]; HRMS Calcd for $C_{14}H_{18}ON$ $(M + NH_4)^+$: 216.1824. Found: 216.1831.

1-Phenylbutan-1-one (3je). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2H), 7.58-7.49 (m, 1H), 7.43-7.41 (m, 2H), 3.09-3.04 (m, 2H), 1.88-1.82 (m, 2H), 1.07-1.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 132.5, 130.8, 130.7, 124.3, 46.8, 19.7, 15.3. Cl-MS *m/z* 166 [$(M + NH_4)^+$, 100]; HRMS Calcd for $C_{10}H_{16}ON$ $(M + NH_4)^+$: 166.1708. Found: 166.1705.

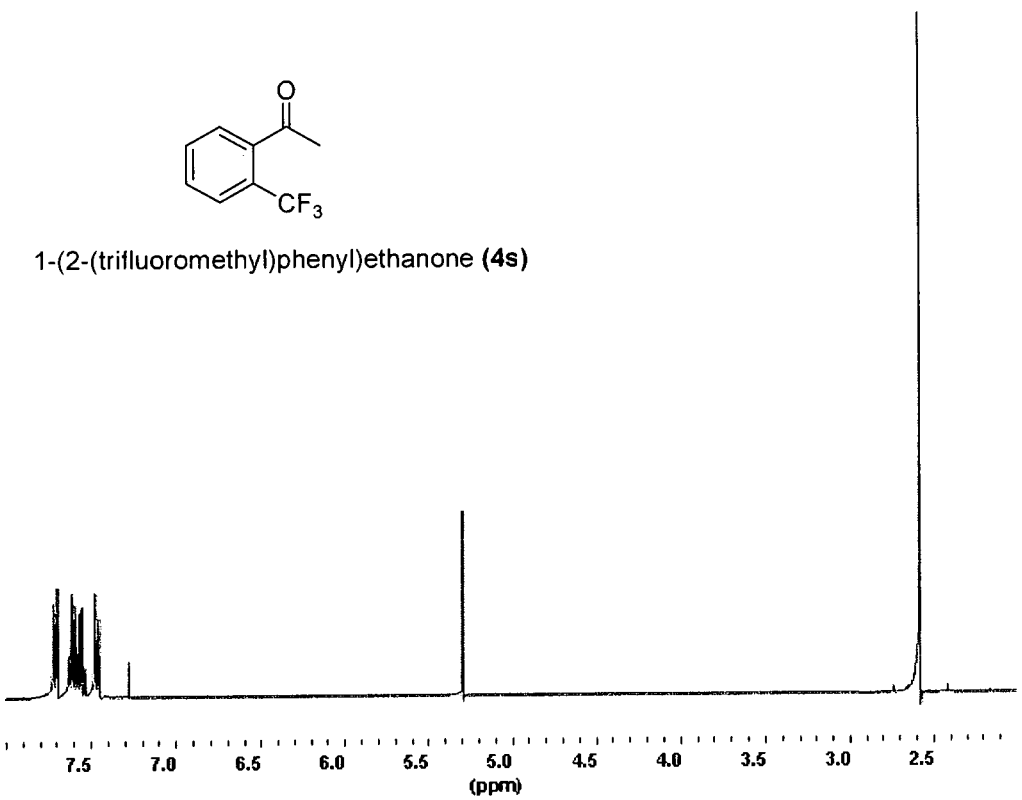
5.6. Sample ^{1}H NMR spectra (400 MHz, $CDCl_3$)

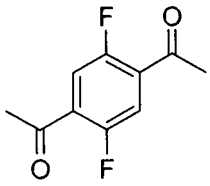


1,1'-(naphthalene-1,4-diyl)diethanone **(4y)**

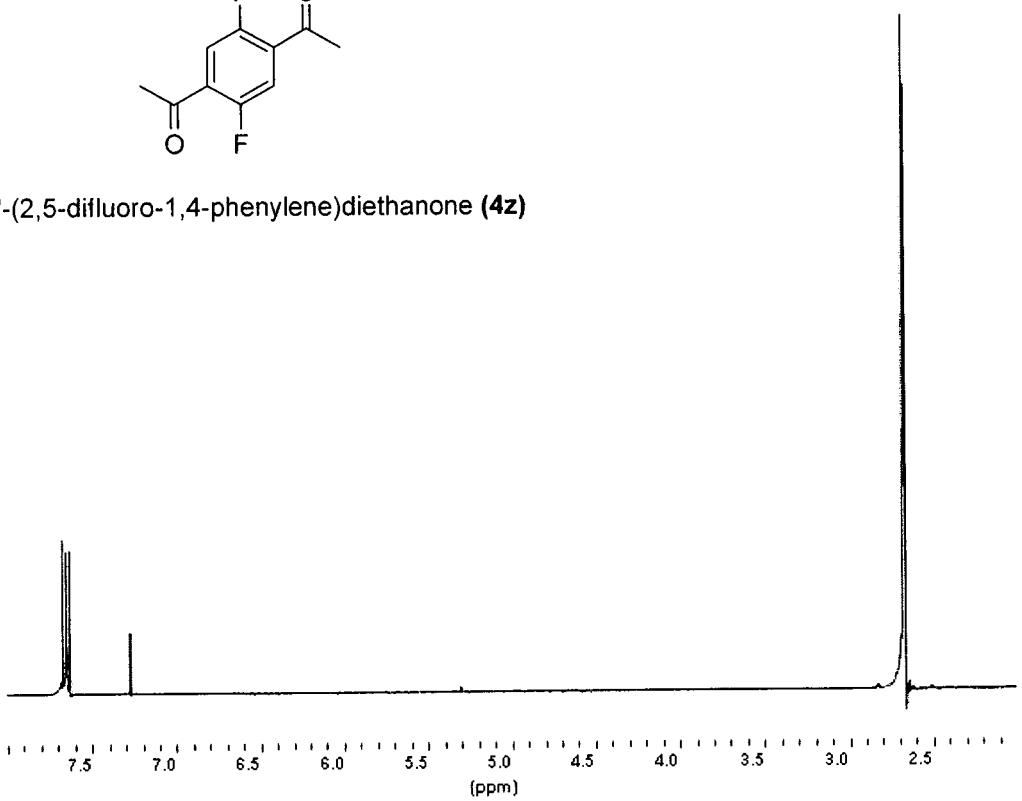


1-(2-(trifluoromethyl)phenyl)ethanone **(4s)**

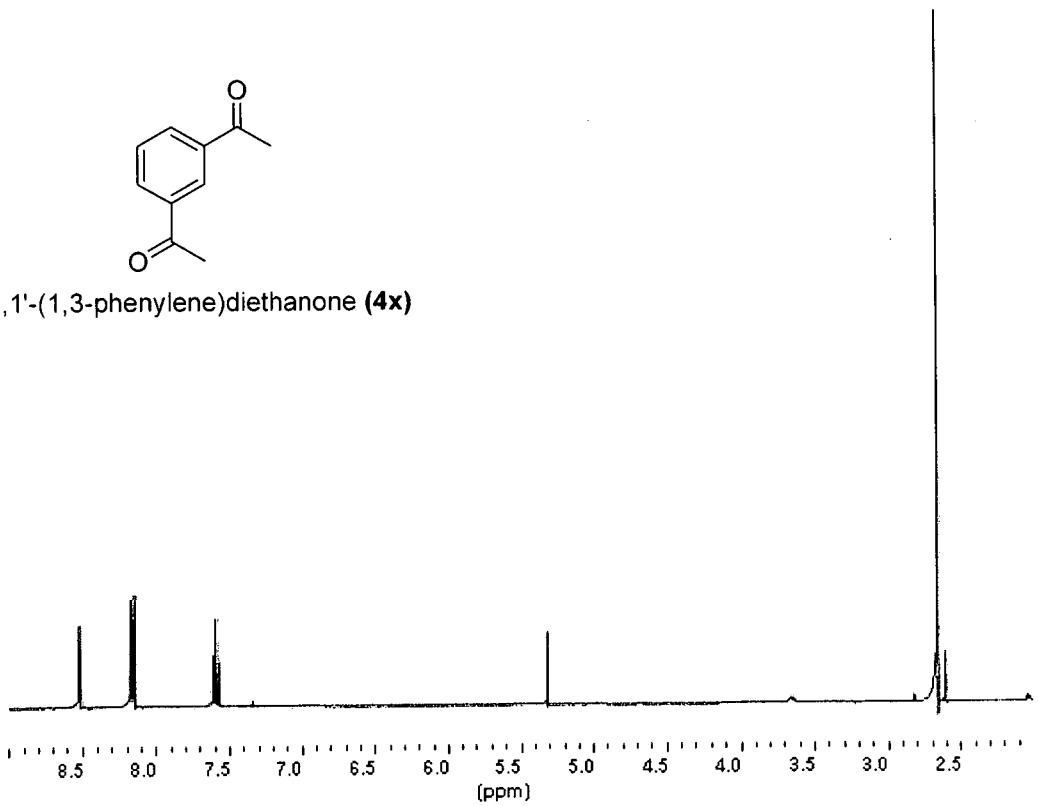




1,1'-(2,5-difluoro-1,4-phenylene)diethanone **(4z)**



1,1'-(1,3-phenylene)diethanone **(4x)**



CHAPTER SIX

General Conclusions and Future Directions

6.1. Regioselective Arylation of Electron-Rich Olefins

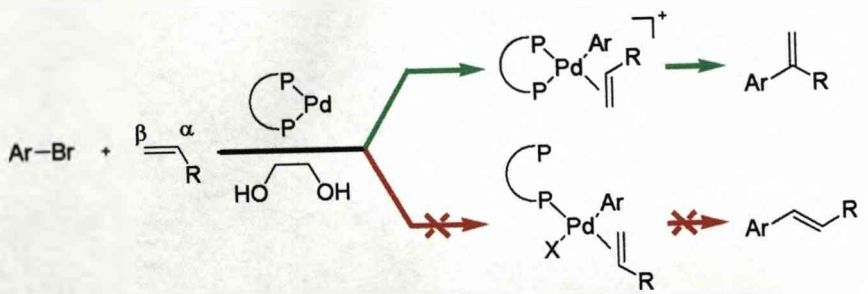
One of the principles of green chemistry concerns explicitly catalytic chemistry, which states: "Catalytic reagents (as selective as possible) are superior to stoichiometric reagents". The underlying idea of this principle is that, owing to catalysis, the minimisation of the resources consumed and the economy of atoms is effective. However, a practical overview of the huge field covered by the term "catalysis" shows that the so-called "catalyst amount" ranges from substoichiometric to amazingly low quantities.[359]

The past several years has witnessed great strides in developing active productive catalysts,[21,140,151,152,155,171,175,177,233,297,321,394] but these catalysts in general do not lead to regioselective reactions in Heck arylation of electron-rich olefins with aryl halides. For electron-rich olefins, arylation most frequently is carried out by employing commercially inaccessible aryl triflates and, when aryl halides are chosen, stoichiometric amounts of silver of thallium salts are generally needed. In 2001, the preliminary work by the Xiao group showcased the unique property of ionic liquid in combination with $Pd(OAc)_2$ and DPPP, which led to an excellent catalyst system which enabled the regioselective Heck arylation of electron rich olefins by butyl vinyl ether.[108] Although only one olefin was shown to be feasible in that paper, it indicated a possibility of affecting the regioselective Heck reaction by using ionic liquid solvents.

From the outset, the aim of the work presented in this thesis was to devise a more efficient catalyst system that would allow for regioselective arylation of electron-rich

olefins by aryl halides. Chapter two saw the introduction of imidazolium ionic liquids for arylation of electron-rich hydroxy vinyl ethers **1e** and **1f**, with the readily available $Pd(OAc)_2$ and DPPP. The arylation not only proceeded with excellent regioselectivity, but circumvented the need for scavengers and use of triflates. Previous reactions using triflates in DMF took 144 h to complete compared to 8 h in ionic liquids.[192] Ionic liquid is termed a "green" solvent as it avoids the use of solvents commonly employed in coupling reactions which are seen as potentially hazardous to the environment. Still questions remain unanswered concerning the toxicity or long term effects of ionic liquids to health and in our ecosystems. Therefore, one must ask whether a solvent where important questions remain unanswered can truly be termed "green".

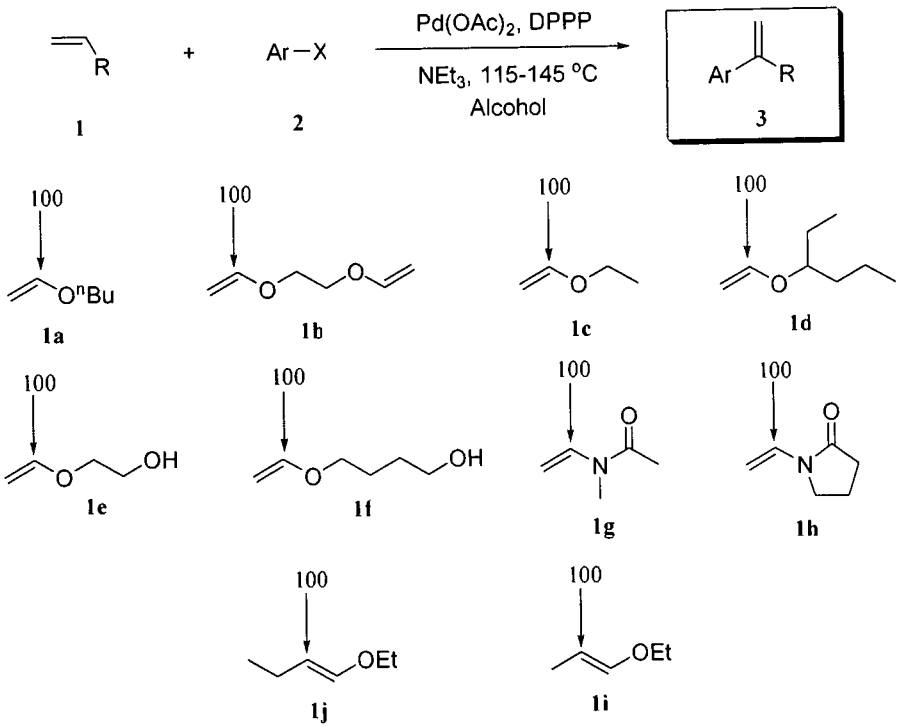
The knowledge gained from our research of hydrogen-bond donor salts led to our investigations in isopropanol.[200] Vinyl ethers **1a-1f** were successfully arylated using the Pd/DPPP catalyst system. In order to expand the substrate scope further, it was found the ethylene glycol was an excellent solvent for the arylation of olefins **1a-1f,** enamides **1g-1h**, and substituted olefins **1i-1j** (Scheme 6.01).



Scheme 6.01. The regioselective Pd-DPPP-ethylene glycol system.

Previously, enamides have required an ionic liquid-solvent cocktail for arylation to occur. A alteration in technique visibly changed the catalyst stability, by possibly inhibiting or slowing down the formation of palladium black, making Pd more readily

available. The reasons behind lie on the foundations in which the H-bond donor salt was successful, and the -OH moiety may be able to acts a halide "scavenger" potentially binding to the dissociating Br^-. Excellent regioselectivities and yields were obtained, again, with no recourse to scavengers or triflates, and no sign of the linear product. Scheme 6.02 summarises the results obtained, highlighting the regioselectivy observed in alcohols.



Scheme 6.02. The regioselective Heck reaction of electron-rich olefins by aryl bromides in alcohol.

Chapter five saw the system performing at extremely low catalyst loadings, which have never been seen before for this family of olefins. Loadings of 0.005% could be achieved for the arylation of a series of dibromides, as well as heterocycles, successfully yielding the branched product at catalyst loadings of 0.1% in just 0.5 h.

Apart from the ideal "solventless" system, or water as the solvent, short chain alcohols are considered to be the next best thing. Isopropanol and ethylene glycol as solvents provide a cheap, effective and efficient alternative to commonly employed molecular solvents. The system allows facile product separation and an immaculately clean reaction, with the possibility of recycle.

The intentions at the beginning of this thesis were to devise an economical, efficient and green catalyst system for the arylation of electron rich olefins by aryl halides. The journey from ionic liquids, through to hydrogen bond donor salts, to now simply using a H-bond donor alcohol solvent, has provided a simple but robust system which exceeded expectations, allowing reactions to be completed in just 24 h at loadings of 0.005% Pd. At a time where prices of precious metals are rising to meet the current financial climate, the market price of palladium is ever increasing (in 1976 the price of palladium was $50/oz, in 2008, $250/oz). Our method in ethylene glycol is therefore a viable, cost-effective process.[395]

6.2. Future Directions

As demonstrated in this work, Pd-DPPP and ethylene glycol form an excellent catalyst system which can perform at extremely low catalyst loadings without the use of expensive ligands or catalysts. Further investigation for this catalyst system for a wider range of reactions can be carried out. An interesting observation made when coming to the end of my studies is that, when using allylamine as a coupling partner with aryl bromides, the C-N coupling products were obtained rather then the expected arylation at the double bond. This would be a very interesting direction to pursue, given the harsh conditions usually applied for C-N coupling reactions.

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